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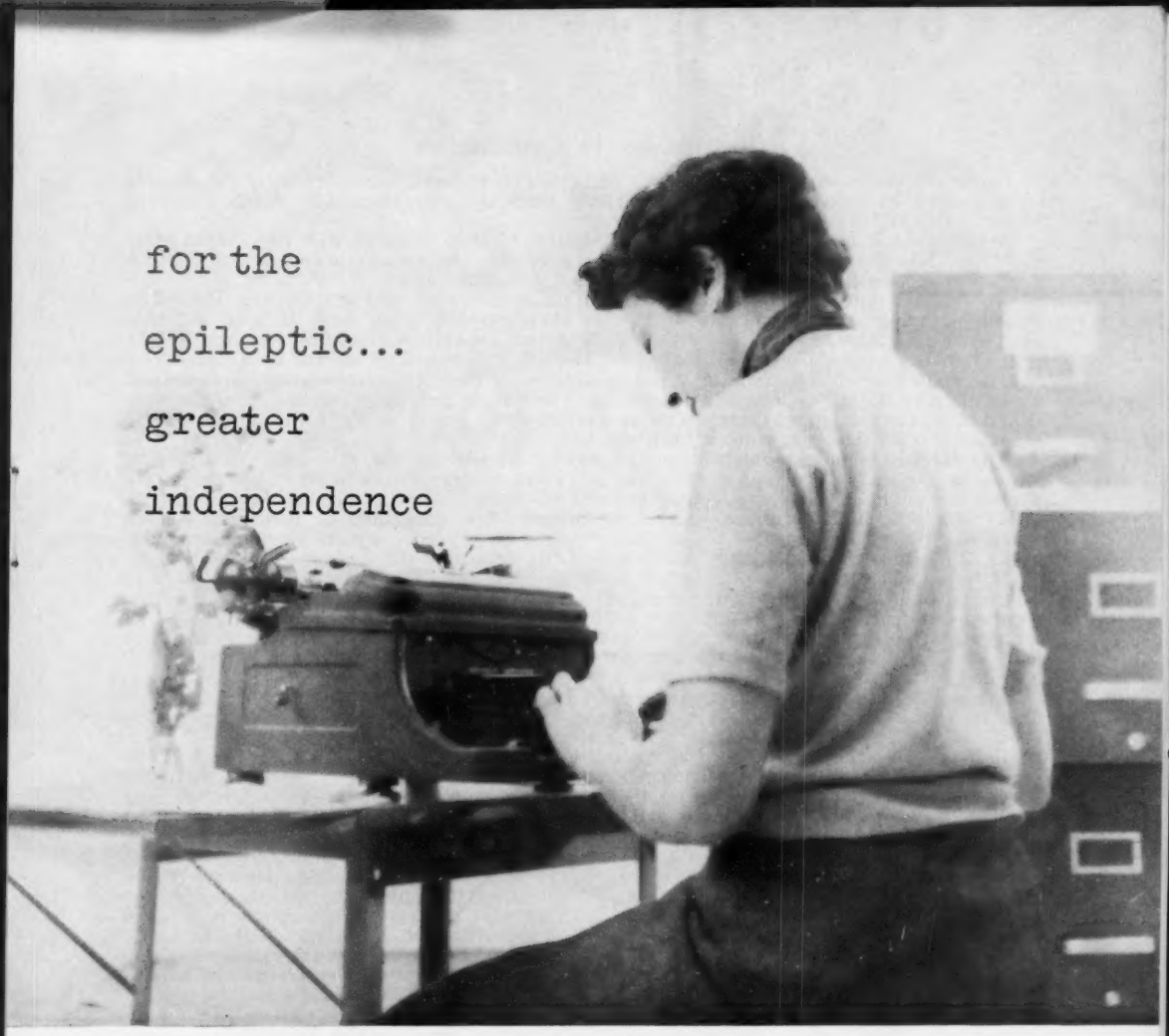

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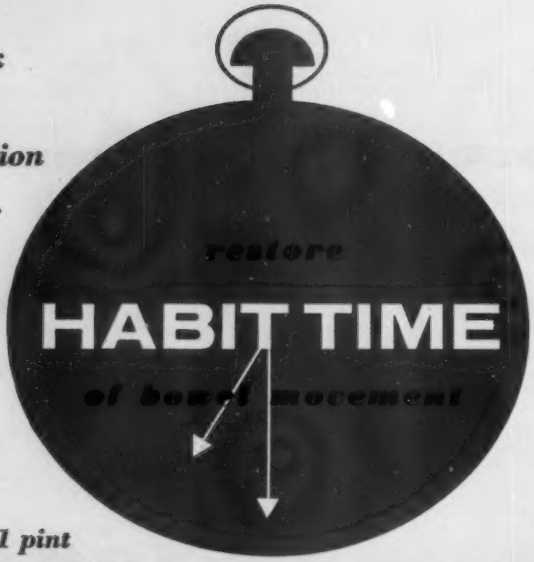

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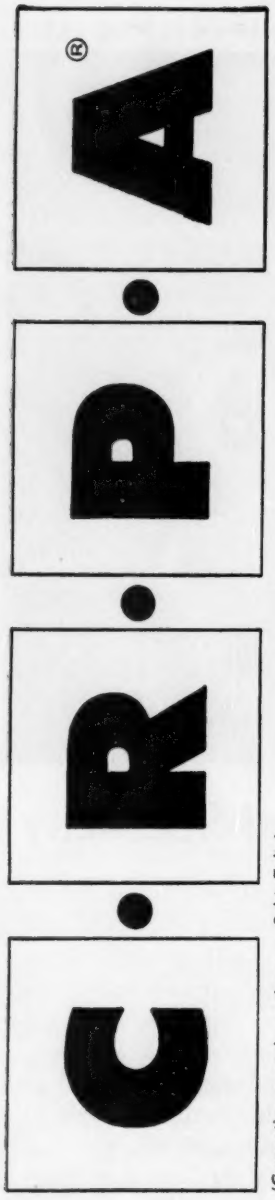

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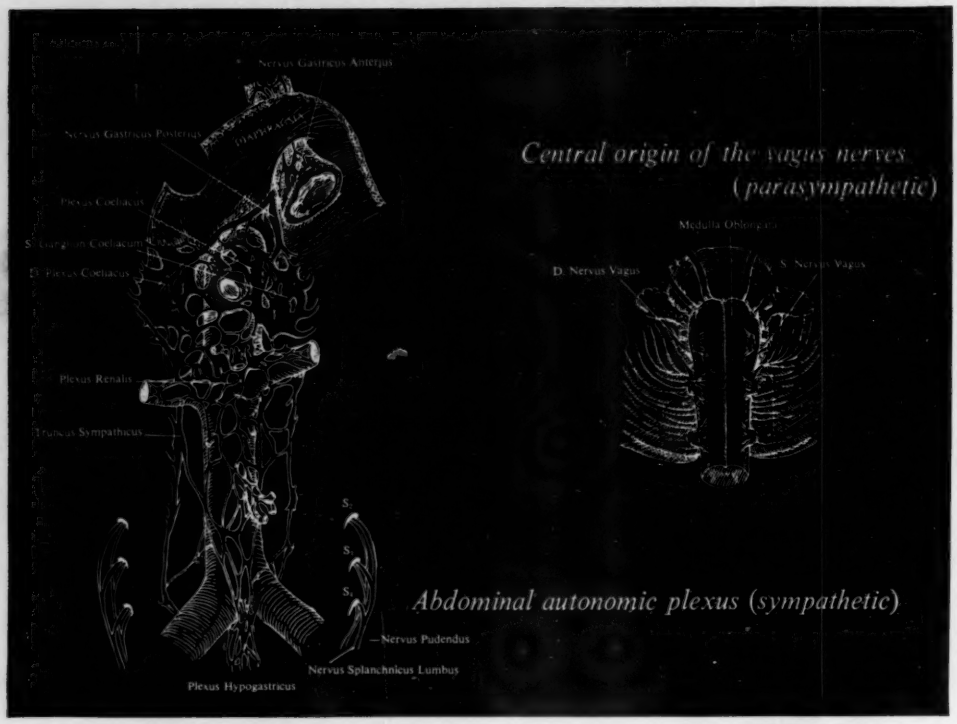

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SEARLE

Renal Factors in Regulation of Electrolyte Balance

L. G. WELT, M.D., Chapel Hill, N. C.

The many processes that are involved in renal physiology are intimately concerned with, and exquisitely adjusted to, the homeostasis of the body fluids with respect to volume, tonicity, composition, and acid-base relationships. The kidney is able to subserve the interests of homeostasis only because it possesses mechanisms which are sensitive to stimuli arising within the organism as a whole. These stimuli, in turn, are either specific deviations from normal per se or some secondary expression of these abnormalities.

The functional unit of the kidney is the nephron, of which there are about 2,000,000 in two organs. This is portrayed in a schematic fashion in Figure 1. The glomerulus is composed of capillary loops through which water and the noncolloidal solutes diffuse and are filtered. The volume of the glomerular fluid, an ultrafiltrate of plasma, formed in a day by an average adult is approximately 180 liters. The volume of finally elaborated urine which reaches the bladder is about 1.5 liters in the same 24-hour period. The bulk of the glomerular water and solutes is obviously reabsorbed, and, in addition, some solutes are secreted by the tubular cells.*

From the Department of Medicine, School of Medicine, University of North Carolina.

Read in the Symposium on Electrolyte and Water Balance before the Section on Experimental Medicine and Therapeutics at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 22, 1954.

* References 1 and 2.

A current concept of renal physiology implies that about 85% of the filtered solutes and water is reabsorbed in the proximal tubule. It is believed that the solutes are actively reabsorbed and, as they are abstracted, the fluid remaining in the tubule is

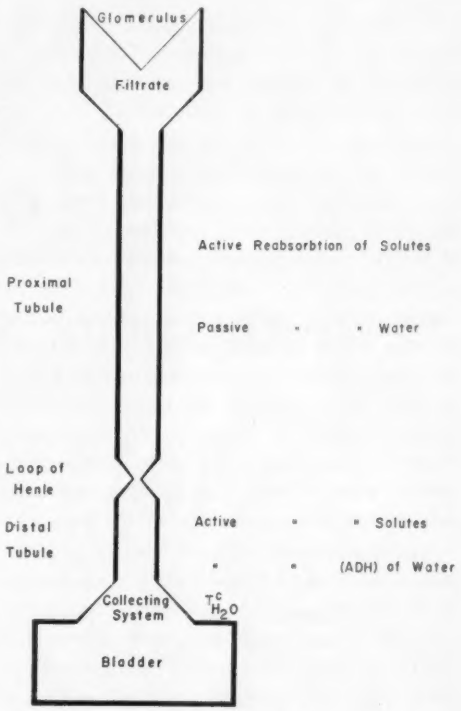

Fig. 1.—Schematic representation of a single nephron.

thereby made dilute. In this fashion a gradient is established for water, and this solvent then diffuses in a passive manner through the tubular epithelium and gains access to the interstitial fluid and eventually to the

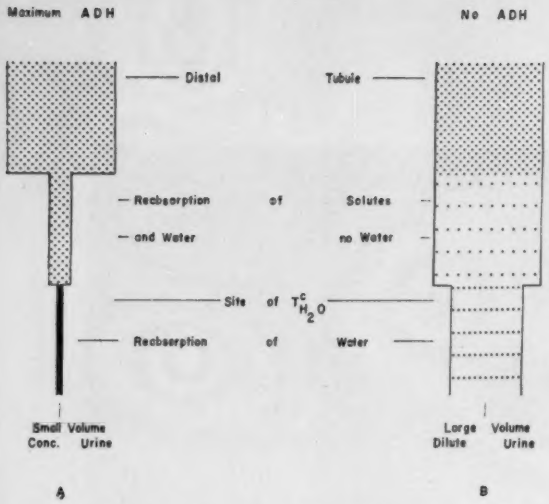

Fig. 2.—Dual process of reabsorption of water in distal tubule, with and without antidiuretic hormone (ADH).

blood draining the kidney. This passive reabsorption of water is termed "obligatory," since it is determined and controlled by the active reabsorption of solute.†

Approximately 15% of the volume of the filtrate, altered in composition but with unchanged total solute concentration, reaches the distal tubule. In this portion of the nephron the active reabsorption of solute does not obligate the consequent diffusion of water. In fact, the implication is quite the reverse, and it is suggested that water is reabsorbed under the influence of the antidiuretic hormone (ADH) of the posterior pituitary gland. Moreover, the reabsorption of water appears to be limited by factors concerned with (1) rate and (2) a maximal concentration of solutes in the tubular fluid.‡

The limitations imposed by these parameters are such that, even when the influence of ADH is maximal, the rate of excretion of urine is not necessarily low nor is the total solute concentration of the urine necessarily high. Thus, in addition to ADH, the rate of excretion of solutes is an important determinant of the volume and concentration of the urine. As the rate of excretion of solutes is accelerated, the rate of excretion of water is increased, and the solute concentration of the urine approaches that of the parent glomerular filtrate.[7]

† References 3 and 4.

‡ References 5 and 6.

It is most difficult to reconcile these observations with a unitary theory of distal tubular reabsorption of water. An alternative hypothesis has been suggested (Fig. 2) which implies that the active reabsorption of solutes in the distal tubule is followed by the reabsorption of an equivalent volume of water under the influence of ADH. In this manner the volume of the distal tubular fluid is diminished but the total solute concentration remains unchanged (Fig. 2*A*). In the absence of ADH the reabsorption of solutes is not accompanied by a reabsorption of water; hence, the tubular fluid becomes dilute but the volume remains unchanged (Fig. 2*B*).§

Following either of these operations the fluid reaches a more distal mechanism where water is reabsorbed without solute. This has been referred to as $T^c_{H_2O}$, and it has been suggested that the site may be in the upper portions of the collecting system of the kidney.[4] At this more distal site, water is reabsorbed to a maximum of 7 cc. per minute, or until the total solute concentration is 1,200 to 1,400 mOsm. per liter, depending on which occurs first. In Figure 2*A* the urine is maxi-

§ References 4 and 8.

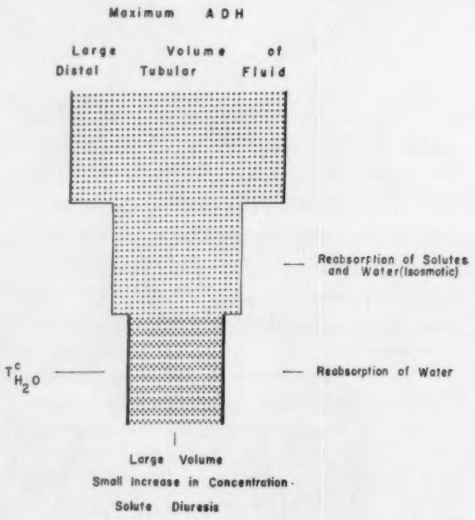

Fig. 3.—Influence of large excretion on the rate of excretion and concentration of urine.

mally concentrated and scant in volume. In Figure *2B* the urine is dilute and large in volume. These two illustrations represent the extremes of concentration and dilution of the urine.

There are a variety of circumstances characterized by the accession of more than 15% of the volume of the glomerular filtrate to the distal tubule. This occurs whenever some limitation is imposed on the reabsorption of solutes (and, hence, water) in the proximal tubule. Such a situation is represented by the filtration of more glucose than can be reabsorbed, as is commonly encountered in patients with diabetes mellitus when there is significant hyperglycemia. To the extent that glucose is not reabsorbed, and to the extent that this interferes with the reabsorption of NaCl, less water is reabsorbed.[4] Thus, an unusually large volume of isosmotic fluid reaches the distal tubule (Fig. 3). Solutes are reabsorbed approximately to the same extent as is implied in Figure *2A*. This is accompanied by the reabsorption of an equivalent volume of water under the influence of ADH. The remaining fluid, unusually large in volume and with unchanged concentration of solutes, gains access to the $T^c_{H_2O}$ site, where 7 cc. of water is abstracted per minute. However, since the volume of fluid that reaches this locus is so large, the loss of this volume of $T^c_{H_2O}$ leads to a relatively small increase in the total solute concentration. Thus, despite maximum ADH activity, the rate of excretion of water is high, and the solute concentration is only minimally increased above that characterized by the glomerular filtrate.

The most important stimulus responsible for the secretion of the antidiuretic hormone of the posterior pituitary gland is an increase in the effective osmotic pressure of the extracellular fluids (or its necessary consequence, the dehydration of cells.)[6] Since sodium and its salts contribute more than 90% of the effective osmotic pressure of the extracellular fluids, it can be said that an increase in the concentration of sodium in the serum promotes, and a decrease in concentration suppresses, the secretion of the antidiuretic hormone.

A stimulus of secondary importance is concerned with the volume (or some function thereof) of a key part of the extracellular space. A contracted volume stimulates, and an expanded volume inhibits, the secretion of ADH.‖

Thus, the hyponatremia induced in a normal subject by the ingestion of water suppresses the secretion of ADH and promotes a large flow of dilute urine. In contrast, the same degree of hyponatremia will not induce a water diuresis in a subject with a significant contraction of the extracellular volume. Although the hyponatremia suppresses the secretion of ADH, the contracted volume promotes its secretion. The net effect is, presumably, the resultant of the two opposing forces, hypotonicity and contraction of the body fluids.

The factors that influence the rate of excretion of salt are even less well understood than those governing water. A diminished rate of filtration of sodium due to either (1) a decrease in the volume of filtrate formed [4] or (2) a decrease in the concentration of sodium in the filtrate [11] promotes an increase in the rate of reabsorption of sodium and chloride. Although the concentration of sodium in the serum influences the rate of excretion of this ion, the particular circumstances that condition a specific concentration of sodium appear to be more important. An increase in the concentration of sodium induced by an infusion of a hypertonic solution of NaCl is associated with an increase in the rate of excretion of salt. However, the same level of hypernatremia that arises as a consequence of a loss of water in excess of salt is associated with a decreased rate of excretion of sodium and chloride. A depressed concentration of sodium in the serum due to the loss of salt in excess of water is accompanied by a diminished excretion of salt. In contrast, the same degree of hyponatremia induced by an infusion of a hypotonic solution of NaCl is accompanied by an augmented rate of excretion of these two ions.

‖ References 9 and 10.

An analysis of these data in an effort to define the factors that may be operative in promoting or restraining the excretion of salt reveals that those circumstances associated with an expanded volume of extracellular fluid are accompanied by an augmented rate of excretion of salt. In contrast, a contraction of the volume of the extracellular space promotes a decreased rate of excretion of salt. It will be noted that this design is the reciprocal of that concerned with the regulation of the excretion of water.

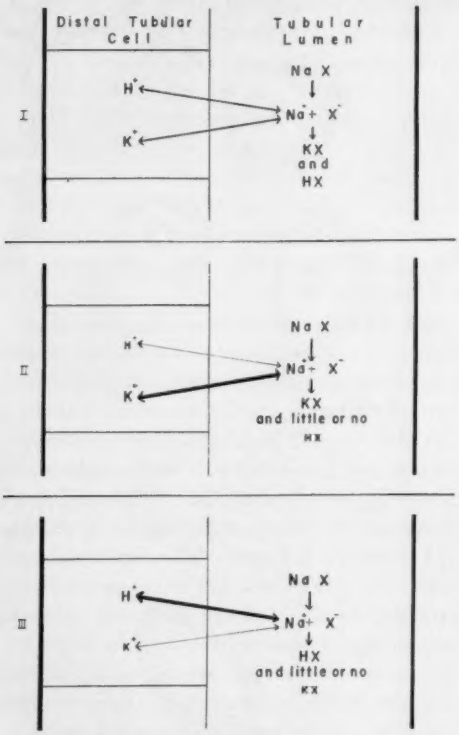

Fig. 4.—The exchange of hydrogen and potassium ions for sodium ion in the renal tubule.

The specific manner in which alterations in volume become effective stimuli and the manner in which these stimuli are implemented ultimately to influence the activity of the renal tubular cells are unknown. The colloid osmotic pressure of the plasma may be one of the stimuli; there may be nervous pathways terminating in the renal tubular cells, and the hormone of the adrenal cortex may influence specific transport mechanisms in the cells of the nephron.¶

The reabsorption of sodium is not always associated with the reabsorption of an anion. A significant fraction of the reabsorption of sodium appears to be associated with the simultaneous secretion of a cation—potassium, hydrogen ion, or ammonium. This process is referred to as an ion exchange. The factors that specifically condition which of these cations will be secreted in exchange for sodium are not clear. It has been suggested that potassium and hydrogen ions are, in a sense, in competition with each other from this standpoint.[14] This competition may be conditioned simply by the relative abundance of one or the other ion. These competitive exchange mechanisms are illustrated in an oversimplified fashion in Figure 4. Panel I suggests that under some circumstances the reabsorption of a certain amount of sodium is associated with an exchange of relatively equal amounts of potassium and hydrogen ions, which then mate with the anions deserted by sodium and are excreted into the bladder. Panel II portrays a situation wherein the relative availability of hydrogen is less than that of potassium. This might be achieved either by inducing a systemic alkalosis by hyperventilation or by administering an alkaline salt. In these circumstances potassium can compete more successfully in the exchange mechanism and more of this ion than of hydrogen is secreted. This sequence of events is one of the factors responsible for the augmented rate of excretion of potassium during alkalosis. Panel III describes the reverse of Panel II. In this instance, hydrogen ions are more available than potassium ions. This might be due to a deficit of potassium, or it might represent a systemic acidosis. At any rate, hydrogen ion competes more sucessfully in the exchange for sodium, and the urine may contain considerable acid. These considerations explain the "paradox" of the excretion of an acid urine despite a systemic alkalosis if there is a significant deficit of potassium.

¶ References 12 and 13.

The reabsorption of bicarbonate appears to be dependent on the secretion of hydrogen ions.[15] This is portrayed in Figure 5. The reabsorption of sodium is accompanied by the secretion of hydrogen ions. The sodium associates with the bicarbonate in the tubular cells, gains access to the interstitial fluid, and is ultimately reabsorbed into the blood stream.

Since the secretion of hydrogen ions, the reabsorption of bicarbonate, the acidification of the urine, and the secretion of ammonium and potassium are dependent in large measure on the reabsorption of sodium, it is clear that any influence which tends to diminish the opportunity for the reabsorption of sodium by ion exchange will impose limitations

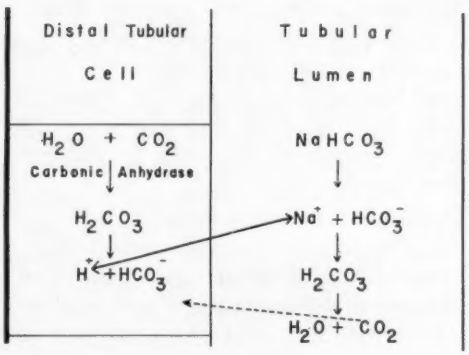

Fig. 5.—The secretion of hydrogen ion and the reabsorption of sodium bicarbonate.

on each of these processes. It may be suggested that the inability to secrete hydrogen, ammonium, or potassium ions may, in turn, impose limitations on the reabsorption of sodium.

This discussion has been too curtailed to detail the list of accomplishments with which the kidney must be credited. Moreover, the amazing and intricate interrelationships and the variations among these that are conditioned by influences that arise from the internal environment, as well as from the kidney itself, make our understanding of renal function appear extremely limited, and, in fact, it is. Nevertheless, there is a body of data from which broad inferences may be drawn, and with these some features of the disorders with which patients suffer may be better understood. This, in turn, can be translated into more meaningful therapeutic terms.

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The Problem of Hypokaliemia

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In clinical usage the terms hypokaliemia and hypopotassemia are taken to indicate a lowering in the concentrations of this ion in serum or plasma below the usual range present in health, even though the words themselves refer to levels in blood. The lower limits of these sets of values are 3.3 mEq. per liter in growing children, in young adults, and in old men and women and above 4 mEq. per liter in newborn infants.* The fact that all of the potassium in serum is ultrafiltrable suggests that it is present entirely in the ionized form.[1] Hence lowered serum levels of this electrolyte can be taken to reflect comparable changes in the potassium concentration of the extracellular fluid as a whole, i. e., in the interstitial spaces as well as in the plasma. Such lowered levels of extracellular potassium may be present without any change in the total amount of extracellular or cellular potassium; they may reflect transfers of potassium into cells, or they may point to losses of cellular and extracellular potassium.

I. ORIGINS OF THE THREE TYPES OF HYPOKALIEMIA

A. Hypokaliemia with Extracellular and Cellular Potassium Intact.—The administration and retention of water or of glucose solutions will understandably dilute the extracellular and the cellular fluids of the body. If potassium is not present in such solutions, the levels of this ion will decrease in cells as well as in the extracellular fluid. Under these circumstances hypokaliemia appears without any external losses of this ion and without evident change in its compartmental disposition (Fig. 1).

Such a change in body potassium concentration will occur in those patients in whom the excretion of water loads is defective, i. e., in patients with oliguria or anuria, as in acute tubular damage or lower nephron nephrosis, or, to a transient or limited extent, in those with adrenocortical insufficiency, cirrhosis and ascites, or congestive heart failure.

B. Hypokaliemia as Result of Movements of Extracellular Potassium into Cells.—A number of mechanisms which result in the movement of potassium into cells have been recognized (Fig. 2). Perhaps the most fundamental of these is the incorporation of this indispensable ingredient of cells during the processes of cell growth or repair.[2] In this regard, substances, such as testosterone, which accelerate protein anabolism have been shown to induce these transfers.[3]

Another set of basic processes which are accompanied by transfers of potassium into cells are those related to carbohydrate metabolism. It has been shown for example that the utilization of sugar by blood cells or by tissue preparations in vitro lowers the potassium content of the suspending medium.† The disposal of exogenous carbohydrate frequently, though not invariably, lowers the extracellular potassium levels.[6] This is attributable in part to the deposition of potassium with glycogen in the liver.[7] In-

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* Danowski, T. S.: Serum Electrolytes in Relationship to Age and Sex, unpublished data.

† References 4 and 5.

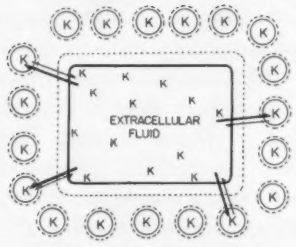

Fig. 1.—Dilution as a cause of hypokaliemia. Dotted lines indicate expansion of extracellular and cellular fluid volumes with potassium-free solutions, thereby lowering the preexisting levels of potassium.

sulin given intravenously in amounts as little as 0.1 unit per kilogram of body weight almost invariably lowers the serum levels of potassium.[8] This presumably reflects participation of this ion in the phosphorylation of glucose and its entry into cells.

There remains a series of miscellaneous and apparently unrelated circumstances in which hypokaliemia results from transfers into cells. Thus, alterations in the pH of body fluids induce potassium shifts: alkalosis removes potassium from cells, whereas acidosis induces transfers into cells.[9] Progressive dehydration is known to result in losses of cell potassium, and hence it is not surprising to find that rehydration reverses this trend.[10] Finally, in familial periodic paralysis the extracellular potassium usually drops prior to or during a seizure. Since this is usually not attributable to losses of the ion in urine, it points to a segregation of extracellular potassium in cells.[11] It is interesting to note, in view of the previous comments on carbohydrate metabolism and potassium transfers, that heavy meals or insulin or glucose administration can precipitate such attacks.

HYPOKALIEMIA AS A RESULT OF K TRANSFERS INTO CELLS.

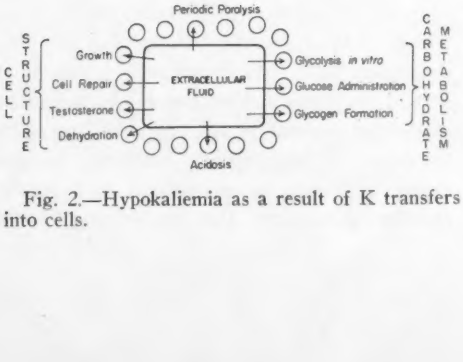

Fig. 2.—Hypokaliemia as a result of K transfers into cells.

C. Hypokaliemia as Result of External Losses.—Body potassium, both extracellular and cellular, can be lost via renal as well as extrarenal routes (Fig. 3).

The continued or increased urinary output of this ion in patients not receiving adequate maintenance amounts of potassium inevitably results in depletion. It has been suggested that this reflects an inherent inability of the kidney to conserve this ion during periods of potassium deprivation.[12] Recent studies in animals and in humans indicate that in health rather precise renal conservation of potassium can be evoked by potassium-free regimens.‡ Hence the renal losses of potassium which occur with gastrointestinal disease, poliomyelitis, and a host of other diseases are mediated through an inadequacy

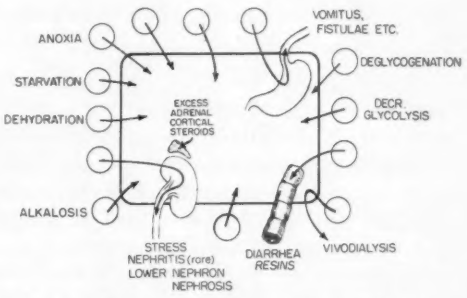

Fig. 3.—Hypokaliemia as a result of K loss from cells and extracellular fluid.

of this conservation response, perhaps as a consequence of changed adrenocortical activity.

Increased renal losses of potassium can also be induced by corticotropin (ACTH) and adrenocortical steroids, by mercurial diuretics, and by carbonic anhydrase inhibitors; they are known to occur in the recovery phase of some patients with lower nephron nephrosis as well as in a limited number of patients with nephritis.[13] In the latter of these two categories the mechanism of loss may well be related to an undue tubular secretion of this ion.

Extrarenal losses of potassium are incurred via vomiting, gastrointestinal drain-

‡ Danowski, T. S.: Renal Conservation of Potassium with Varying Sodium Intake, unpublished data.

age or lavage, diarrhea, cation exchange resins, or vivodialysis.[13]

II. RELIABILITY OF HYPOKALIEMIA AS INDEX OF POTASSIUM DEPLETION

It is immediately obvious from the preceding section that the simple presence of lowered plasma or serum levels of potassium does not establish the existence of potassium deficits outside or inside of cells. However, if dilution and transfers of potassium into cells can be excluded, it is true that the small portion of body potassium present in serum or plasma often reflects similar changes within the larger pool of this ion in cells.[10] Hence such a finding should arouse a high index of suspicion of potassium deficiency.

On the other hand, the presence of normal or even high concentrations of serum potassium does not exclude this possibility, since dehydration will mask such deficits. This is especially clear from studies in infant diarrhea and in diabetic coma.[13] Under such circumstances the understanding of the basic physiology of these disorders, which clearly indicates that deficits are incurred, should take precedence over the absence of hypokaliemia.

III. BIOCHEMICAL AND PHYSIOLOGIC CHANGES IN HYPOKALIEMIA

Rather regularly deficits of extracellular and cellular potassium are accompanied by hypochloremia and alkalosis. This new steady state represents the net effect of an undue loss of acids from the extracellular space by transfers into cells or by excretion via the urine.[10] It is per se of no known or established clinical significance save that it does serve to alert the physician to the presence of potassium deficits. In this regard it should be remembered that the superimposition of renal failure or starvation will mitigate or replace the metabolic alkalosis with a metabolic acidosis. This occurs, for example, in the prolonged vomiting of pyloric stenosis.

Deficits of cellular potassium produced by a number of means produce necrosis of skeletal and cardiac musculature [13] and presumably interfere with cell integrity and function. These may well be the most important deleterious effects of potassium depletion, since they may be crucial determinants of survival or recovery. Experimental animals and patients with hypokaliemia may develop electrocardiographic alterations consisting of various degrees of T-wave depression and Q-T prolongation, as well as muscular paralysis or paralytic ileus.[14]

The above findings are not invariable concomitants of low potassium levels in plasma and hence serve to emphasize the incompleteness of our knowledge. Are the symptoms and signs which develop in such patients correlated with the levels of either extracellular or cellular potassium alone? Is the ratio of the two the determining factor? Does the ionization of cell potassium play a role? What about the associated electrolyte disorders that are frequently present in these patients, or of the medications which are given? In regard to the last two of these it is important to note that hypokaliemia and hypocalcemia tend to mask one another[15] and that hypokaliemia evokes the toxic manifestations of digitalis in patients in whom the maintenance dosage had previously been adequate.[16] These observations point up the need for precise observations which will explain the variable incidence of physiologic changes with comparable degrees of hypokaliemia.

IV. PREVENTION AND THERAPY OF HYPOKALIEMIA

The classification of hypokaliemia into the three categories presented earlier simplifies the prophylactic and therapeutic approach. Dilution hypokaliemia is to be avoided in oliguric patients by limiting water administration to maintenance requirements. The drop in potassium which occurs with transfers of potassium into cells is clinically unimportant save that in periodic paralysis it should be prevented or treated by administration of several grams of potassium salts by mouth at appropriate intervals. In patients with deficits of cellular and extracellular potassium the underlying cause

should be eradicated, if possible. Potassium salts are then given if the patient's condition is too grave to warrant reliance upon gradual replenishment from dietary sources.

SUMMARY

Discussion of the problem of hypokaliemia has been simplified by indicating that dilution, transfers into cells, and external losses can all produce comparable degrees of lowering of extracellular potassium levels. The sporadicity of the known physiologic accompaniments of hypokaliemia, i. e., the electrocardiographic changes, the muscular paralysis, the tissue necrosis, the paralytic ileus, and the interrelations of hypopotassemia and hypocalcemia or digitalis intoxication all indicate that further definition of conditioning factors is needed. In the interim it seems desirable to avoid or correct deficits of body potassium, and of cellular potassium in particular, irrespective of the levels of serum potassium.

125 DeSota St. (13).

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Hyponatremic Syndrome

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The hyponatremic syndrome is a prevalent phenomenon, according to recent reports, perhaps largely owing to the facility with which sodium determinations have been able to be performed by the flame photometer in the last decade. The low-sodium syndrome or, less specifically, the "low salt syndrome" are terms used synonomously. Related to this syndrome are the former descriptions of "hypochloremic azotemia" and also the syndrome of "water intoxication." [1]

The term hyponatremic syndrome implies that there are clinical signs and symptoms which are rather specifically related to a low sodium concentration in the serum and extracellular fluid. In recent years, a low sodium concentration has been found frequently to accompany a wide variety of disease states. This has led to some confusion about the syndrome, since many of the symptoms and signs may be associated with the primary diseases and not necessarily with the incidental finding of low sodium concentration. Thus, the specificity of the clinical symptoms and signs needs careful analysis. If a definition of the syndrome is to be useful, one might hope to develop accurate diagnosis and treatment which would correct specifically the manifestations. Let us approach the problem of definition.

The term low-salt syndrome was first popularized by Schroeder, in describing some patients with cardiac failure and edema with low serum sodium concentrations. Even though the name of the syndrome seemed to put emphasis on sodium, Schroeder stated plainly that this condition could be brought about by dilution of electrolytes from a high water or low salt intake. Thus he might just as well have called it the "salt dilution" syndrome. He postulated that this condition followed the use of mercurial diuretics in conjunction with diets low in sodium chloride and that the administration of concentrated sodium chloride was sometimes corrective.

The dictionary says that the word syndrome means "concurrence" and when used in medicine it is "a group of signs and symptoms that occur together and characterize a disease." The definition of the hyponatremic syndrome needs clarification in at least four important ways.

1. EMPHASIS ON REGULATION OF WATER AS WELL AS SODIUM CONCENTRATION

If the sodium concentration is abnormally low, the water concentration is abnormally high. Equal emphasis upon water and sodium is important, because from the standpoint of etiology it is apparent that the abnormal concentration could be produced either by a loss of sodium or by a gain of water in the extracellular fluid compartment or by both. There is perhaps a tendency today among clinicians to lay the blame on the sodium ion and proceed with therapeutic manipulation of sodium intake, at the same time adhering to the therapeutic principle of water intake being forced or water given ad libitum.* We must look with suspicion upon the mechanisms for regulation of water as well as for sodium metabolism.

2. THE PROBLEM OF INTERNAL INTERCOMPARTMENTAL SODIUM AND WATER BALANCE REGULATION

Secondly, the terms "low" or "high" do not specify in what part of the body sodium

Read in the Symposium on Electrolyte and Water Balance before the Section on Experimental Medicine and Therapeutics at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 22, 1954.

* References 2-4.

and water are increased or decreased. It is conceivable that a low concentration, without alteration in total body content, could be produced by a shift of sodium into cells and/or shift of water out of cells.† In addition, the size of the intravascular compartment or the blood volume may be important in the production of some of the circulatory abnormalities of the syndrome.‡ We must examine the mechanisms responsible for the balance of electrolyte and water across the internal boundaries—namely, the capillary and the cell walls. This may be called the problem of internal intercompartmental balance regulation.

3. IMPORTANCE OF OTHER ELECTROLYTE ABNORMALITIES

Third, we have a problem of defining whether certain clinical signs and symptoms are specifically related to alterations in sodium concentration. In many of the diseases accompanied by low sodium concentration there may also be a derangement of potassium concentration and frequently a depletion of intracellular potassium. In some cases we might reasonably ask if abnormalities of other electrolytes, for example, of magnesium, may be responsible for some of the symptoms. Furthermore, parts of the clinical picture may be modified by the relative concentrations of chloride to sodium and by the presence of acidosis or alkalosis. All electrolyte abnormalities which accompany the hyponatremia must be examined.

4. EXTERNAL BODY SODIUM AND WATER BALANCE REGULATION

Fourth, and last, the description of any hyponatremic situation should include knowledge concerning the direction of external total body sodium and water balances. Some patients with hyponatremia can excrete administered sodium and water normally; others cannot. It is not enough to know only how much or how little sodium and water is being excreted by the kidneys or lost by other routes. We must know what proportion of the intake is being lost. We cannot determine by analysis of serum sodium concentration alone how the over-all regulation of body sodium or water balance is being conducted. A few determinations of total dietary intakes and total urinary sodium and water outputs are worth more than several serum concentration determinations when managing the condition. Estimation of water balance may be more difficult than that of sodium because of variation in insensible water loss, but it is nonetheless important in determining the picture.

The points so far considered important in the description of any hyponatremic situation may be summarized as follows:

I. External total body balance regulation of sodium and water
   - (*a*) Influence of magnitude of intake
   - (*b*) Renal control of excretion [17]
   - (*c*) Insensible loss and loss by gastrointestinal tract

II. Internal intercompartmental balance regulation of sodium and water
   1. Intravascular ⇄ extravascular, extracellular
      - (*a*) Hydrostatic capillary pressure
      - (*b*) Tissue pressure and elasticity
      - (*c*) Serum protein concentration
      - (*d*) Blood loss
   2. Extracellular ⇄ intracellular
      - (*a*) Cell energy and osmotic control [18]
      - (*b*) Influence of hormones
      - (*c*) Malnutrition
      - (*d*) Acid-base balance
      - (*e*) Anoxia

III. Associated electrolyte derangements
   - (*a*) Potassium
   - (*b*) Chloride
   - (*c*) Magnesium §
   - (*d*) Metabolic or Respiratory acidosis or alkalosis [23]

The factors involved in the regulation of internal intercompartmental balance and of external balance are listed, as well as possible associated electrolyte abnormalities. Of course, it is much easier to list these factors than to determine them in each case.

I shall here attempt to outline the clinical physiological pathology of the hyponatremic edematous cardiac patient, drawing a little

† References 5-7.

‡ References 8-16.

§ References 19-22.

from my own experience and using as much information as I could find from the work of students on this subject. The factors are summarized as follows:

A. Clinical features
1. Older patient
2. Severe failure
3. Prolonged failure
4. Poor prognosis
5. Cirrhosis of liver (cardiac)‖
6. Inelastic tissues
7. Previous low-sodium diets [24]
8. Previous mercury diuresis
9. Malnutrition
10. Water given, forced or ad libitum

B. Physiological features
1. Low serum sodium concentration
2. Low serum chloride concentration (metabolic alkalosis)
3. Azotemia, progressive
4. Low serum proteins
5. Water antidiuresis
6. Sodium antidiuresis [33]
7. Cell potassium decreased [14]
8. Total nitrogen deficit ¶
9. Cell sodium increased.
10. Cell water increased #
11. Abnormal thirst mechanism
12. Low blood pressure*
(peripheral circulatory insufficiency)

C. Symptoms
Nonspecific
1. Weakness, drowsiness, lethargy, apathy
2. Anorexia, nausea, occasional vomiting †
3. Mental confusion, psychosis, coma
Specific
1. Thirst
2. Muscular and abdominal cramps
3. Convulsions, twitchings [39]

D. Response to therapy
1. Unresponsive to sodium restriction
2. Unresponsive to more digitalis
3. Aggravated by excess water intake
4. Unresponsive to mercury or
5. Mercury diuresis of potassium with chloride (low potassium toxicity occasionally) [40]
6. Thirst with water restriction
7. Thirst with sodium administration
8. Rise in serum sodium without diuresis on administration of large doses of potassium [41]

E. Response to concentrated NaCl administration
1. Usually disappointing, no diuresis [42]
2. Demonstrates large sodium space (cellular plus extracellular)
3. Mercury responsiveness, increased diuresis due to excess available chloride [43]
4. More edema (if water not restricted)

There are many other situations besides that of the edematous cardiac patient in which hyponatremia occurs. Each of these situations must individually be characterized in terms of the internal and external balance behavior. The many situations are listed below, and many have been studied extensively with experimental and clinical methods.

1. Tuberculosis ‡
2. Malnutrition
3. Hypoadrenalism
4. Postoperative overhydration §
5. Hypodermoclysis overhydration ‖
6. Heat cramps, water intoxication
7. Gastrointestinal salt loss
8. Nephrosis
9. Cirrhosis of liver ¶
10. Hypoalbuminemias
11. Pitressin administration #
12. Renal disease, salt loss *
13. Miscellaneous injuries and illness [55]
14. Experimental dialysis †

CONCLUSION

The hyponatremic syndrome of the edematous cardiac patient is caused primarily by a failure of the mechanisms for maintenance

‖ References 25 and 26.
¶ References 27 and 28.
# References 29 and 30.
* References 31 and 32.
† References 34-38.

‡ References 44 and 45.
§ References 46 and 47.
‖ References 12 and 48.
¶ References 49-51.
# References 32 and 52.
* References 53 and 54.
† References 56 and 57.

of proper proportions of sodium, chloride, potassium, and water in all body fluid compartments. Its onset is accelerated by low-sodium diets, mercurial diuretics, and high water intake. The mechanisms failing are those that selectively control intake; namely, thirst and appetite, those that control selective renal excretions, and those which preserve the internal structure of cells.

No ready solution to the problem and no therapy which is specific can be offered. The best treatment is to avoid it. Many cases are irreversible and represent in the patient with cardiac failure a final dissolution of the mechanisms for regulating body fluid structure.

There are many other hyponatremic situations, which should not be confused, as regards origin and mechanism, with the syndrome of the edematous cardiac patient.

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Problems of Electrolyte and Water Balance in Nephrotic Syndrome

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Patients complaining of an insidious onset of edema and showing heavy proteinuria, a low serum albumin concentration, and high blood fats and cholesterol present the cardinal manifestations of the nephrotic syndrome, or lipemic nephrosis. Current ideas on the etiology, pathology, and treatment of this syndrome have been summarized in recent reviews.* The underlying pathology is in the kidneys, and the first aim of treatment is to promote the healing of the renal lesion, on which the ultimate outcome depends. During the course of the disease, numerous secondary manifestations may appear. In the early stages we commonly see oliguria, retention of sodium and water with edema, and alterations in the concentration of sodium, potassium, or calcium in the blood. Later, especially in those patients with destructive renal lesions, there is progressive azotemia, with acidosis, anemia, and hypertension.† Today we are to consider the disturbances of water and electrolytes in the nephrotic syndrome. Even though we know that these changes are secondary to the underlying pathology, their recognition and treatment are important for the patient's well-being and for safe and effective use of hormonal therapy.

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* References 1-3.

† References 4-6.

CONSEQUENCES OF GLOMERULAR LESION AND PROTEIN LOSS

In the nephrotic syndrome the glomerular filter becomes more permeable to protein, especially to the plasma albumin.‡ The loss of circulating albumin leads to a reduced plasma volume.[9] The impairment of general circulation is seldom obvious, but there may be evidences of peripheral vasoconstriction, with pallor despite a high hematocrit level; orthostatic hypotension and syncope may occur. Partly owing to the reduction in circulation, and partly owing to the glomerular lesion, there is a reduction in glomerular filtration rate.§ In the normal nephron a large volume of fluid is filtered and reabsorbed so as to allow for concentration of wastes in the urine. When the tubular load is decreased by falling filtration, the kidney becomes a less efficient excretory organ. The elimination of water and sodium is impaired.‖ In addition to the reduction in filtration, the reduced circulating volume stimulates antidiuretic activity and also leads to secretion of the sodium-retaining corticosteroid, aldosterone, by the adrenal cortex.¶

The physician can follow one of three general courses in planning treatment. He may wish to minimize the collection of edema by a low-sodium diet and by the use of ion-exchange resins or diuretics. These measures have not proved uniformly effective in relieving edema, and they may lead to an undesirable depletion of electrolytes. When the edema is massive, it may be relieved by

‡ References 7-10.

§ References 6, 11, and 12.

‖ References 1, 6, and 12.

¶ References 13 and 14.

paracentesis or the use of Southey's tubes. Secondly, the plasma volume may be increased by the use of albumin or other osmotically active agents, such as dextran, which generally result in diuresis in about 50% of cases. This approach can be used effectively as a temporary means of improving circulation and renal function. Recently, there has been increasing use of the adrenal cortex hormones, which offer both a high probability of diuresis, with correction of most of the manifestations of the nephrotic syndrome, and a chance that the underlying condition may be improved.[3]

EDEMA AND HYPONATREMIA

In a group of edematous patients who entered the hospital for treatment of the nephrotic syndrome the serum sodium was frequently reduced in concentration (Fig. 1). Weakness, anorexia, disturbances of thirst, hemoconcentration, and impaired renal function # were present in a number of these patients, but these symptoms and signs were not clearly related to hyponatremia alone. Many of these patients had been on diets low in sodium and on various programs designed to eliminate sodium from the body. Nevertheless, edema remained while the serum sodium concentration fell. This situation demonstrates an impairment of water excretion, which may be related to the low plasma volume, to antidiuretic substances, or to renal failure. In a patient who is accumulating edema rapidly, the use of a very low sodium intake serves only as a mild brake on water accumulation, and hyponatremia is likely to result. Paracentesis frequently produces a sharp fall in serum sodium concentration unless a free intake of sodium is given. Restriction of water intake is contraindicated when renal function is reduced, and the administration of hypertonic saline solution is rarely helpful. The development and resolution of this problem may be illustrated by a case history.

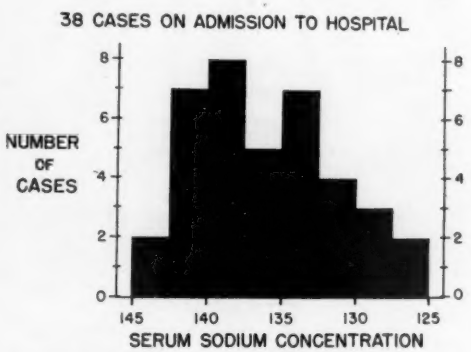

Fig. 1.—Serum sodium concentration in patients with the nephrotic syndrome on admission to hospital. The majority of patients had levels below the lower limits of normal (less than 138 mEq. per liter).

A 16-year-old girl came to the hospital with edema due to lipemic nephrosis. We planned to give her a course of treatment with corticotropin (ACTH). She had been on a diet containing sodium chloride, 1 gm. per day, but had continued to show a steady gain in weight. She was observed for four days in the hospital, while she deliberately restricted her fluid intake to less than 1 liter per day. Weight gain slowed, but urine volume fell to very low levels. The blood urea and serum potassium increased, while the serum sodium remained low. Figure 2 shows that the urine contained almost no sodium during this period and that there was retention of potassium at the low urine volume. The serum potassium was too high to allow the safe institution of corticotropin treatment. It was deemed essential that kidney function be improved. A gradual increase in water intake resulted in accumulation of fluid and a gain in weight. Urine flow increased slowly; renal function improved, and the serum potassium fell, but, at the same time, edema increased and there was a further fall in the serum sodium concentration. This last disturbance could have been avoided by the administration of more sodium, but edema would have been further increased. Concentrated human serum albumin was used with good effect under these conditions to produce increased diuresis and an elevation of the serum sodium, even though the total quantity of edema fluid removed was not large.[12] The patient then received treatment with corticotropin, which was followed by diuresis, elimination of edema, and, ultimately, healing of the renal lesion.

Oliguria and water retention are often aggravated during the first few days of administration of cortisone or corticotropin.* These changes are not dependent on sodium retention, for they may appear while sodium balance is unchanged. Indeed, if less than 3 to 5

References 15 and 16.

* References 17-19.

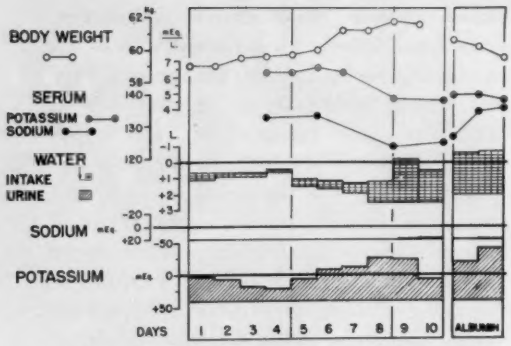

Fig. 2.—Effects of reduced water intake (Days 1 to 4), increasing water intake (Days 5 to 10), and concentrated human serum albumin (25 gm. intravenously twice daily) in a 16-year-old girl with lipemic nephrosis. Body weight and serum sodium and potassium concentrations are shown by the points in the upper three lines. Intake of water, sodium, or potassium is indicated below each zero line, and the output is plotted up from the intake. A clear space below the zero line shows that intake exceeds output (positive balance), while extension of the output above the zero line shows loss (negative balance).

gm. of sodium chloride is given each day there may be an undesirable depression of serum sodium concentration. In extreme cases, frank water intoxication, with headache, nausea, mental confusion, muscle hyperirritability, convulsions, hypertension, pulmonary edema, oliguria, and azotemia, may occur. Figure 3 shows moderate retention of water out of proportion to sodium during corticotropin therapy. The resulting fall in serum sodium is reversed promptly with the onset of diuresis at the end of treatment,

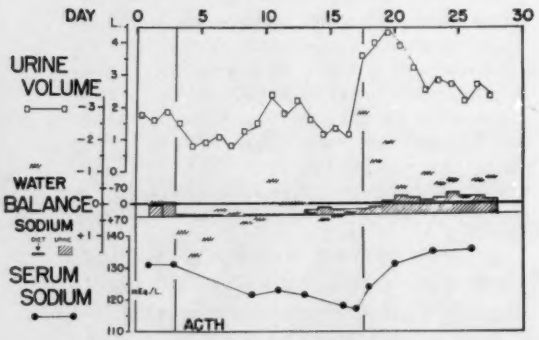

Fig. 3.—Oliguria and retention of water resulting in reduced serum sodium concentration during corticotropin therapy followed by improvement with diuresis. Water balance, indicated by the wavy line, shows larger changes than sodium balance, resulting in dilution of the extracellular sodium.

when water is eliminated without sodium until the serum sodium concentration returns to normal.

ABERRATIONS OF SERUM POTASSIUM

It has been pointed out that a low urine volume may be associated with potassium retention and a rise in the serum potassium concentration. We have also seen that a fall in urine volume may occur during the early stages of cortisone or corticotropin treatment. If an adequate urine flow is not established before adrenal cortex hormones are given, the increase in serum potassium may be so threatening as to require temporary cessation of hormone therapy. Figure 4 shows the combined effects of increased appetite and

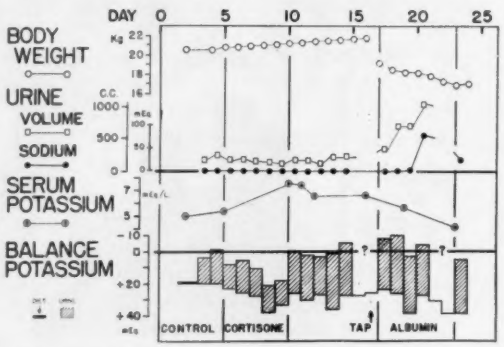

Fig. 4.—Retention of potassium with oliguria during cortisone administration; subsequent elimination of potassium with diuresis on intravenous administration of concentrated human serum albumin.

intake of potassium, of reduced urine flow and output of potassium, and of the antianabolic effect of cortisone, which were followed by a rise in serum potassium. The potassium concentration returned to normal when renal function and diuresis were improved after administration of concentrated human serum albumin. This example serves as a warning against the routine prescription of added potassium salts to patients receiving the adrenal cortex hormones. Patients with oliguria or impaired renal function may be unable to cope with an increase in potassium load during this time.†

When urine volume increases, there is a greater tendency to eliminate potassium. A

† References 17 and 19-21.

very sharp change in balance may occur within a few days. Figure 5 shows a dangerous fall in the serum potassium level which accompanied profuse diuresis in a patient under treatment with corticotropin. The early days of treatment were accompanied by a satisfactory potassium balance, but with the onset of rapid diuresis very large losses of potassium occurred. On the third day of diuresis this patient was discovered to have muscular weakness, diminished tendon reflexes, a slow irregular heart action, and electrocardiographic changes characteristic of hypokalemia. Prompt and heavy replacement of potassium was necessary to correct the severe potassium depletion. It is notable that this change occurred quite abruptly in a patient who was under close observation. It is obvious that potassium chloride, 3 to 5 gm. per day, should have been added to the patient's ordinary intake as soon as diuresis increased, since the patient was not able to conserve potassium normally in the presence of a rapid urine flow and a high level of adrenal corticosteroids.

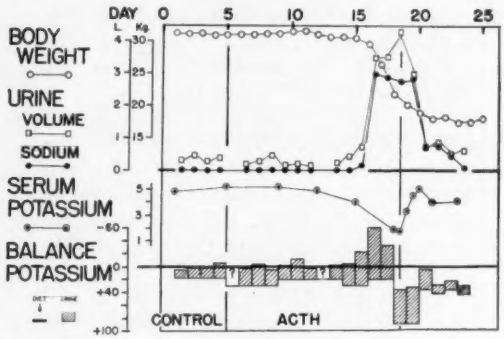

Fig. 5.—Severe potassium depletion following diuresis in a 7-year-old boy receiving corticotropin. Administration of corticotropin was stopped. Potassium chloride (6 gm. per day) was given to bring total intake to 90 mEq. daily.

COMMENT

The electrolyte disturbances which have been described are secondary to the underlying disease and disappear promptly with improvement in the renal lesion. Nevertheless, such disturbances may produce serious signs and symptoms unless they are promptly recognized and treated.

Simple observations of body weight, fluid and food intake, urine flow, and renal function give important clues, which allow the anticipation and prompt treatment of some of these troubles.

Regimens designed to eliminate an excess of sodium from the body are useful only if water is eliminated also. If a patient continues to show oliguria and to accumulate water, with resultant gain in weight, even a moderate reduction in sodium intake may lead to reduction of serum sodium. Under the circumstances, the repeated and ineffectual use of diuretics and paracentesis usually leads to severe and symptomatic depletion of sodium out of proportion to water. A more fundamental attack on the impairment of water balance is required. The desired result can often be temporarily accomplished by the use of concentrated human serum albumin or other osmotic agents capable of expanding the plasma volume.[12]

Potassium balance is less easy to predict, but the general principles are well known. Oliguria and impaired renal function diminish the output of potassium, and so the plasma level may rise under the load of increased intake or of release from the body cells following cellular injury or catabolism. Depletion of potassium may occur when the intake is inadequate to supply the anabolic requirements of the cells plus losses in the urine or in the stools. When cortisone or corticotropin is given, the serum potassium may rise when urine volume is low and later fall sharply when urine flow increases. During the use of these hormones, we usually withhold added potassium salts for a few days, until a normal urine flow appears, and then add increasing doses of potassium chloride as diuresis increases. Close observation of the serum potassium concentration is helpful, especially when urine volume is changing rapidly. The specific electrocardiographic changes ‡ which accompany potas-

‡ References 22 and 23.

sium intoxication or depletion are useful in guiding treatment in severe derangements of potassium balance.

SUMMARY

Many patients with the nephrotic syndrome show abnormalities of serum sodium concentration, related to their disease and to therapeutic measures aimed at the control of edema. Disturbances of potassium balance are less common but may develop rapidly to a level which causes neuromuscular and cardiac embarrassment. Measures are described for the control of these electrolyte abnormalities.

Clay and Webster Sts. (15).

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Management of Congestive Heart Failure

Management Designed to Avoid Serious Disturbances of Electrolyte and Water Balance

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The term "congestive heart failure" identifies a clinical syndrome characterized by at least three components: First, there is venous congestion of the pulmonary or systemic circulations, usually both but sometimes separately; second, there is usually retention of salt and water by the kidneys, resulting in edema, and, finally, these processes are causally linked with a failure of cardiac function. Restoration of cardiac compensation by measures which act directly on the heart, such as digitalis, often results not merely in improved cardiac function, as evidenced by a rise in cardiac output and a shrinkage in heart size, but also in the relief of venous congestion and the renal excretion of edema fluid. Although edema formation is a secondary consequence of cardiac failure, it has become increasingly apparent that the relief of edema by measures which have no direct effect on the heart may also eventuate not merely in a striking improvement in clinical symptomatology but in a betterment in cardiac function as well. Hence, agents such as mercurial diuretics, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide (Diamox; acetazoleamide), acidifying salts, etc., which have as their primary object the relief of edema, a secondary manifestation of cardiac failure, and their primary locus of action not the heart but the kidneys, constitute an extremely important therapeutic adjunct in the treatment of congestive heart failure.

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In addition to the relief of edema these measures have serious toxic potentialities, producing at times profound derangements of the body fluids, which, in turn, can inhibit further response to therapy and result in profound clinical deterioration or even death. The purpose of the present report is threefold: to describe certain relevant physiological features inherent in the process of edema formation; to distinguish, on this basis, the type of diuretic measures available for the management of congestive heart failure, and, finally, to define the toxic and therapeutic effects of diuretic measures in the context of known principles of renal function and electrolyte metabolism, so as to obtain a rational evaluation of both their beneficial and their deleterious properties.

The extracellular volume comprises two principal fluid spaces: the intravascular space, or blood volume, and the interstitial fluid. Edema represents an expansion of one phase of the extracellular compartment, the interstitial fluid. The volume of this compartment may expand as a result of two processes: 1. As a consequence of the failure of the heart, there is a rise in central venous pressure which acts as a continuous force promoting a transudation of fluid out of the vascular channels and into the interstitial spaces. This type of edema is characterized by a redistribution of extracellular fluid: the plasma volume contracts and the interstitial volume expands, but the total extracellular volume remains unchanged. 2. As a response to the redistribution of extracellular fluid, the kidneys may retain salt and water, causing thereby an expansion not merely of interstitial fluid but of the total extracellular compartment as well.

In certain instances of pure left ventricular failure, the high venous pressure in the pul-

monary circuit promotes segregation of fluid in the lungs, but the renal retention of salt, so prominent a feature of ordinary congestive heart failure, does not occur. The pulmonary edema is, therefore, distributional in type. It is important to recognize that in certain forms of heart failure the extracellular space in the systemic circulation may not expand. Aggressive attempts to produce diuresis with such measures as mercurial diuretics, which are designed primarily to accelerate the renal excretion of salt, may succeed only in drastically reducing the volume of extracellular fluid without necessarily alleviating pulmonary congestion. This is one cause of the low-salt syndrome which may be attributed to misdirected therapeutic effects.

In most instances of heart failure, however, renal salt and water retention is a prominent feature. It is generally agreed that the removal of edema fluid is desirable because the pain, discomfort, and impaired appetite associated with congested viscera and the unsightliness caused by the swelling are removed. Far more important, however, are the relief of dyspnea and the improved cardiac function which follow successful diuresis. Presumably this improvement is due to a fall in venous pressure associated with the diminution of edema. As a consequence, cardiac function and pulmonary congestion improve. Pugh and Wyndham,[1] for example, noted a fall in right auricular pressure and a rise in cardiac output in association with a diuresis produced by a mercurial diuretic in a patient with congestive heart failure. It is, therefore, of the greatest importance to promote the removal of edema fluid at the same time that precautions are taken to avoid or minimize disturbances in body fluids which are themselves deleterious.

TYPES OF DIURETIC MEASURES

It has previously been pointed out that generalized edema develops because a disequilibrium of Starling forces, caused by the high central venous pressure, promotes a transudation of fluid out of the blood into the interstitial spaces, in response to which the kidneys retain salt and water. Diuretic measures may promote the excretion of edema fluid either (1) by correcting the dislocation in the Starling equilibrium responsible for the renal retention of salt or (2) by influencing the dietary intake or renal excretion of salt and water directly, so that more is excreted than gains access to the body. It should be recognized, of course, that although both groups of measures produce a negative balance of salt, only the measures in the first group accomplish this by correcting the factors causally involved in the production of edema.

In Table 1 the diuretic measures in the various categories are listed. This list is not intended to be exhaustive. Osmotic diuretics, such as urea or glucose, have not been included, because the evidence that they deliver edema fluid into the urine in significant amounts is unconvincing.[2] Similarly, massive water loads as a diuretic measure have been omitted because a water diuresis does not usually significantly accelerate salt excretion either in normal subjects [3] or in patients with edema [4]; moreover, forcing massive amounts of water may result not merely in nausea and vomiting but in water retention,[4] eventuating in a low-salt syndrome—hyponatremia, azotemia, weakness, lethargy.

TABLE 1.—*Diuretic Measures of Value in Treatment of Congestive Heart Failure*

I.	Diuresis produced by correcting the disturbance of the Starling equilibrium responsible for edema formation
	A. Digitalis
	B. Postural changes and bed rest
II.	Diuresis produced by diminishing dietary intake of salt
	A. Low-salt diets
	B. Cation exchange resins
III.	Diuresis produced by accelerating renal excretion of salt
	A. Mercurial diuretics
	B. Ammonium chloride
	C. Acetazoleamide
	D. Potassium salts
	E. Xanthines

Digitalis and Bed Rest.—The bulk of evidence militates against any significant direct action of digitalis bodies upon the kidneys. Therefore, digitalis is of avail as a diuretic

only in the presence of heart failure. Of all the measures available for the promotion of diuresis, digitalis is the most physiological, in that it facilitates the excretion of edema by improving cardiac function directly, thereby removing the causal factor which initiates the congestive state. Moreover, successful digitalization may relieve symptoms of cardiac failure even when a salt retention syndrome does not develop, and when no generalized expansion of extracellular volume has supervened. Finally, a digitalis diuresis is always physiological, in the sense that disturbances in composition of body fluids or excessive excretion of extracellular fluid never result. For all these reasons, digitalis is probably the most important and least hazardous measure in the treatment of congestive heart failure. In addition to its therapeutic value, digitalis is an excellent diagnostic tool. If the cause of edema is not apparent, the development of a diuresis following digitalization establishes the existence of congestive heart failure, inasmuch as digitalis will promote the removal of no other type of edema.

As an adjunct to digitalis, rest is invaluable. Some patients in failure will actually regain compensation with bed rest alone. It favors the dissipation of edema for two reasons: 1. Fluid segregated in the legs is transferred into the general circulation, and thereby made available for excretion; if orthopnea or paroxysmal nocturnal dyspnea are present, rest in bed should be accomplished with the patient in a semisitting position to avoid a transfer of fluid from the legs into the lung parenchyma with the assumption of a supine position. 2. The decreased load on the circulation resulting from a more nearly basal state may increase the efficiency of the heart. Although bed rest has been thought to favor the development of pulmonary emboli, this danger can be minimized in the cardiac patient by permitting the free movement of his legs without depriving him of the benefits which bed rest affords.

In some patients during their initial attack of decompensation, and in many patients who subsequently fail despite successful earlier treatment, readjustment of digitalis dosage and rest may be insufficient to restore compensation. Moreover, certain types of congestive heart failure—those resulting from an acute myocarditis or cor pulmonale—respond poorly to digitalis. Measures must then be resorted to whose primary aim is to relieve edema. These prevent the formation or diminish the volume of edema by minimizing the access of sodium salts to the body or by inhibiting their renal tubular reabsorption so that excretion is enhanced. The prime indication for these measures is not heart failure per se but the presence of a salt-retention syndrome. If the latter has not supervened (and, at times, particularly in left-sided failure, it does not), these measures are of little value and may actually prove harmful by diminishing extracellular volume below normal or altering extracellular composition.

Restriction of Dietary Salt and Water.—Irrespective of the cause of edema or the measures employed to promote its elimination, the restriction of dietary salt is an important therapeutic adjunct, because edema fluid is an ultrafiltrate of plasma containing approximately 140 mm. of sodium salts for every liter of fluid and the kidneys will not usually retain water unless salt can also be retained in these proportions. Since the excretion of salt by edematous patients is often less than 1 gm. a day, the low-salt diet must be extremely rigorous for optimum effect; in some communities tap water contains such high concentrations of sodium that the maximum effects of salt restriction may not become apparent until distilled water is substituted in cooking as well as drinking. If the amount of salt in the diet can be reduced below that excreted in the urine, salt and water will be lost from the body and edema fluid will be mobilized. Usually this is not possible because the reabsorption of salt by the renal tubules is so complete that an essentially salt-free urine is excreted, containing less than is present in even a rigorous salt-free diet. Nevertheless, even if the relief of edema can not be achieved, rigid salt restriction may prevent or certainly retard

the formation of further edema. Once an edema-free state has been attained, it may often be maintained by salt restriction alone, without additional diuretic measures.

Rigorous salt restriction is not without potential hazards. Actual salt wastage may develop in some patients—particularly patients with hypertensive vascular disease and renal insufficiency—who are placed on rigorous low-salt diets when they do not have any tendency toward salt retention. A mounting azotemia, signs of shrinkage of extracellular volume, hyponatremia and hypochloremia, and ultimately salt depletion shock are indications that the kidneys can not conserve the normal body stores of sodium during the stress of rigorous salt restriction. The administration of salt results in both clinical improvement and recession of azotemia. Occasionally, the same sequence of events may ensue in an edematous patient. When salt is available freely in the diet, some of it is retained by the kidneys under the stimulus originating from the congestive state; when salt is rigorously restricted, the impaired capacity of the renal tubules to reabsorb sodium may be uncovered, with an insidious depletion of extracellular volume resulting. In edematous patients with renal insufficiency whose edema is successfully controlled by rigid low-salt diets, the absence of clinical evidences of salt depletion and laboratory evidences of azotemia and hyponatremia or hypochloremia should be periodically ascertained.

If the intake of salt is restricted in patients with generalized edema, they may be permitted free access to water for two reasons: 1. Patients without a significant intake of salt tend spontaneously to curtail their intake of water. 2. Excessive intakes of water will be excreted, because ordinarily the kidneys will not retain water without equivalent amounts of salt. Restriction of water (except for short periods in connection with the administration of hypertonic saline solution) is contraindicated. Water deprivation results not in a delivery of edema fluid from the body but in a drastic reduction in urine flow. The retention of sodium by the kidneys becomes more intense [4]; azotemia may supervene.

Cation Exchange Resins. — These substances are extremely stable high-weight polymers containing reactive groups (either hydrogen or ammonium) which exchange for various cations in the gastrointestinal tract. Because of these exchanges, two consequences arise which account for the beneficial as well as deleterious effects of resins: 1. The cation bound to the resin is excreted in the stool. This may result in the removal of significant amounts of sodium, and thereby prevent or at least retard further edema formation. However, the loss of other cations—calcium, and especially potassium, for which resins have a greater affinity than for sodium—may cause deficits of these substances. 2. The hydrogen or ammonium which is released from the resin by the cation exchange is absorbed from the intestine as HCl or NH_4Cl. Here, again, this action may be beneficial, since the acid load may promote the excretion of sodium into the urine as well as potentiate the action of mercurial diuretics. In the presence of renal disease, however, the kidneys may be unable efficiently to excrete acid, and so a severe high-chloride acidosis may result.

Early studies indicated that resins were relatively ineffective in promoting fecal losses of sodium in edematous patients on low-sodium diets and stressed instead their capacity to decrease significantly sodium absorption on higher sodium intakes.* More recently, however, it has been demonstrated that resins can promote the excretion of large quantities of sodium in the feces despite rigorous low-salt diets.† After edema clears, however, the uptake of sodium by the resin becomes quite small,[8] perhaps as a consequence of a decreased secretion of sodium and an increased secretion of potassium into the lumen of the gastrointestinal tract.‡ Nevertheless, the small amounts of sodium

* References 5-7.

† References 8 and 9.

‡ References 8 and 10.

that continue to be removed via the stool plus the accelerated urinary sodium excretion resulting from the acidifying effect of the resin is extremely effective in preventing the reaccumulation of edema, providing that rigid salt restriction is continued. If the salt intake is increased only slightly, edema reappears.[11]

The major hazards of resin therapy appear to be the following: 1. The depletion of body stores of essential cations. Despite the incorporation of resins in the potassium cycle in commercially available preparations, prolonged use has resulted in the development of potassium deficiency, § especially when potassium intake has been curtailed by anorexia or potassium loss has been accelerated by vomiting, diarrhea, and probably mercurial diuretics as well. Calcium deficiency, as manifested by hypocalcemia, has also been observed. || Tetany is exceedingly rare in instances of hypocalcemia, probably because of the presence of a mild systemic acidosis. 2. A high-chloride acidosis may develop in patients with renal insufficiency when the capacity to secrete acid into the urine is impaired. 3. On rare occasions, a clinically symptomatic hyponatremia ("low salt syndrome") has supervened,¶ apparently because the removal of sodium by the resin may not be accompanied by the excretion of equivalent amounts of water by the kidneys. Here, too, patients with serious renal insufficiency may be especially vulnerable. 4. Azotemia has also, infrequently, developed during resin therapy.# This may be a consequence of the continued insidious loss of sodium after edema has disappeared, reducing extracellular volume below normal values. 5. Finally, distressing gastrointestinal symptoms may arise—bloating and abdominal discomfort, anorexia, nausea, vomiting, and diahrrea or constipation.

In order to maximize the benefits or resin therapy and minimize its hazards, the following points should be borne in mind: 1. Only preparations containing some resin in the potassium cycle should be used for the treatment of edema. The usual daily dose of the commercially available preparations ranges between 40 and 100 gm., the precise amount being limited by the development of excessive gastrointestinal symptoms. 2. To prevent or correct electrolyte disturbances, patients should be closely watched for evidences of potassium deficiency (especially in the presence of anorexia, vomiting, diarrhea, or mercurial diuresis), acidosis, hyponatremia, and salt depletion; periodic examinations of the blood for sodium, potassium, bicarbonate, chloride, and urea should be performed. If resin therapy is of long duration, the serum calcium should also be ascertained. A minor degree of hyperchloremic acidosis is very common, but if the serum bicarbonate should fall below 20 mEq/L., discontinuance of the resin should be seriously considered.[9] More serious acidosis, with stupor, Kussmaul respirations, and azotemia, may require the administration of alkalinizing salts in addition. Potassium deficiency can be corrected by adding potassium salts to the patient's fluid intake. Since potassium deficiency can develop slowly and insidiously during resin therapy and may not be accompanied by a fall in serum potassium, supplemental potassium should be considered if unexplained weakness, unexplained digitalis toxicity, or other clinical evidences of potassium deficit develop. Various clinical features suggestive of potassium deficiency are listed in Table 2. 3. If severe renal disease is present, especially if accompanied by an acidosis, resins should probably not be employed, except where precise chemical control is available. Intermittent administration may be necessary to prevent a serious acidosis. The currently available resins with anion exchanges have not clearly lessened the acidifying effect of resins appreciably. 4. Finally, rigid sodium restriction is essential for optimum effectiveness.

Despite these hazards, resins constitute an extremely useful adjunct in the treatment of generalized edema. They can reduce or even eliminate the necessity for mercurials and

§ References 9 and 11.
|| References 11 and 12.
¶ References 9 and 11.
# References 9 and 11.

other diuretic measures, thereby facilitating a more satisfactory control of edema, since a constant edema-free state may be maintained without the intermittent retention and excretion of salt and water so characteristic of treatment with mercurial diuretics. Should supplementary diuretic measures be occasionally required, the acidifying effect of the resin will enhance the action of mercury. Finally, in patients who are refractory to all diuretic procedures, resins may be the only measure effective in reducing the volume of edema fluid.

TABLE 2.—*Symptoms and Signs of Potassium Deficiency*

I.	Clinical symptoms and signs
	A. Fairly specific
	1. Flaccid paralysis of the extremities (very rare)
	2. Paralysis of the intercostal muscles (very rare)
	B. Highly nonspecific
	1. Extreme weakness
	2. Diminished deep reflexes
	3. Mental apathy or confusion
	4. Chronic ileus with abdominal distention
	C. Intelligent clinical appraisal of circumstances likely to produce potassium loss
	D. Unexplained appearance of digitalis toxicity
II.	Electrocardiographic evidence (nonspecific but suggestive)
	A. QU-interval prolongation
	B. T-wave inversion and ST-segment depression with digitalis toxicity
III.	Chemical evidence
	A. Low concentration of serum potassium
	B. Alkalosis
	C. Presence of a prominent U-wave
	D. Appearance of various arrythmias associated

Mercurial Diuretics.—Digitalis, rest, salt restriction, and resins are often insufficient to rid the patient in severe congestive failure of edema. Under such circumstances, measures are resorted to which promote salt excretion by inhibiting the renal tubular reabsorption of sodium. Mercurial diuretics are by far the most effective diuretic agents which act directly on the kidney. The bulk of evidence thus far assembled suggests that their locus of action is the proximal tubule,* although effects in the distal tubule can not be conclusively excluded.†

There is general agreement about the following points concerning the technique of parenteral administration.‡ Subcutaneous and intramuscular injections are preferable to the intravenous route, because the danger of acute fatal reactions is practically eliminated.[18] The diuretic effectiveness is very nearly the same by all three routes, though diuresis starts and terminates earlier when the injection is intravenous.[18] 2. Five-tenths cubic centimeters should be given as a test dose, especially in elderly patients or patients with renal insufficiency, to test the reaction to diuresis as well as to help gauge the size of future injections. 3. Not more than 2 cc. of a mercurial diuretic should be injected at any one time. Indeed, smaller amounts given more frequently appear to be safer and perhaps more effective.[18] 4. The drug should be injected in the morning to minimize the diuresis during the night and thereby permit the patient a more uninterrupted sleep. 5. Most clinicians give mercurials no more frequently than two to three times weekly. Providing they induce a diuresis, mercurials have been given over prolonged periods at this rate without toxic effects. Some observers have advocated the use of daily injections of mercurials to maintain an edema-free state. The studies of Burch and his associates on the urinary excretion of radioactive mercury have raised considerable doubt about the safety of such a schedule because of the danger of toxic accumulation of mercury.[20] The urinary excretion of mercury in normal subjects still persisted 24 hours after its administration. This lag in excretion, and hence the danger of toxic accumulation of mercury, is greatly enhanced under the following circumstances: (1) congestive heart failure, (2) renal disease, (3) failure to develop a diuresis, and (4) the intramuscular instead of the intravenous route of administration. The period between injections, therefore, should be determined at least in part by these findings.

In Table 3 the contraindications to the use of mercurial diuretics are summarized. It is

* References 13-15.

† References 15-17.

‡ References 18 and 19.

important to emphasize again that the indication for mercury is not heart failure per se but the salt retention that usually accompanies it. In patients whose edema has been successfully relieved or in instances of pure left ventricular failure in which no tendency toward salt retention develops, the repeated administration of mercury, particularly if the patient is on a low-salt diet, may produce a drastic shrinkage in extracellular volume, with weakness, azotemia, and even vascular collapse ensuing. This sequence of events is, fortunately, rare, because patients usually become refractory to mercury when their edema is relieved. At least presumptive evidence of salt retention should be at hand before aggressive mercurial therapy is started.

TABLE 3.—*Temporary or Permanent Contraindications to Use of Mercurial Diuretics*

I.	Acute renal disease, e. g. acute glomerulonephritis
II.	Severe renal insufficiency
III.	Toxic reactions
	A. Hypersensitivity to mercurial diuretics
	B. Mercury poisoning
IV.	Absence of edema
V.	Lack of diuretic response to injections of mercurial diuretics

Failure to develop a diuresis is also an important contraindication to further mercurial injections until the cause of the refractory state can be ascertained and corrected. The repeated administration of mercury where no diuresis is forthcoming may lead to toxic accumulation and renal damage or cause accelerated losses of potassium (instead of sodium) into the urine, with the development of potassium deficiency.

Certain patients, either initially or following a period of satisfactory diuretic response, are refractory to the diuretic action of mercury. Various factors appear to be responsible for this refractory state, some of which have been identified and are listed in Table 4.

Hypochloremic alkalosis and potassium deficiency are both a result of mercurial diuresis as well as a cause of mercurial refractoriness. How this complication is produced by mercury is not clear. Balance data reveal that the urine of patients who develop alkalosis following administration of mercury contains greater amounts of chloride than sodium as compared with their serum concentrations.§ The normal ratio of Na/Cl, in serum (corrected for Donnan effect and serum solids) is about 1.3; in patients who develop hypochloremic alkalosis, ratios as low as 0.3 in the urine have been reported.[22] This excessive loss of chloride is balanced by an accelerated excretion of potassium or ammonium, or both.

To explain this excessive chloride excretion, it has been suggested that the primary effect of mercury is an inhibition of the renal tubular reabsorption of chloride, with sodium, potassium, and ammonium following passively in amounts determined by the regulatory influences governing the tubular transport of these substances.[22] Hypochloremic alkalosis, on this view, would develop when, because the stimulus for sodium retention became intense, excessive amounts of ammonium or potassium instead of sodium were excreted into the urine with chloride.

Such an explanation does not readily account for the fact that many patients excrete sodium and chloride in the proportions found in extracellular fluid. Moreover, like mercury, a glucose diuresis in patients with edema often sweeps potassium rather than sodium into the urine with chloride[2]; yet this could hardly be ascribed to a specific effect on chloride reabsorption. An alternative hypothesis could explain many of these findings by postulating as the primary action of mercury an inhibition of the proximal tubular reabsorption of sodium, which results in the delivery of increased amounts of this cation to the distal tubule. If the capacity of the distal tubule to retain sodium is very great, the increased sodium reaching it may be reabsorbed in exchange for potassium or ammonium, thereby accelerating the excretion of one or both of these substances. As a consequence of this process, hypochloremic alkalosis of three types can eventuate: 1. If ammonium but not potassium is excreted

§ References 21-23.

with the excess chloride, as appears to be the case in some patients,[22] then the alkalosis is the result, in part at least, of a net loss of acid from the body. 2. If potassium but not ammonium is excreted with the excess chloride,[22] there may be a loss of hydrogen (and probably sodium as well) from the extracellular phase into tissue cells in exchange for the cellular potassium which ultimately finds its way into the urine—a process which has been demonstrated in other types of potassium deficiency. || 3. The excretion of both potassium and ammonium may be accelerated. Whichever mechanism is operative, the excretion of large amounts of sodium, potassium, ammonium, chloride, and water in this manner without commensurate amounts of bicarbonate presumably can accentuate the alkalosis by reducing drastically the volume of extracellular fluid in which bicarbonate is dissolved.

Hypochloremic alkalosis should be suspected in any patient whose condition becomes refractory to the action of mercury. The administration of ammonium chloride, orally or intravenously, restores responsiveness. For intravenous use, 500 to 1000 cc. of 1% NH_4Cl in 5% glucose should be injected slowly at a rate not exceeding 150 cc/hr., with constant supervision for such signs of ammonium intoxication as pallor, sweating, collapse, or convulsions. Correction of alkalosis can also be accomplished with the potent carbonic anhydrase inhibitor, acetazoleamide, which, by inhibiting the renal tubular formation of carbonic acid, facilitates the retention of acid. By the judicious combination of acetazoleamide and ammonium chloride, very effective retention of both acid and chloride can be achieved, although careful chemical control is necessary to prevent the supervention of a severe systemic acidosis.

Since potassium deficiency (with or without a depression of serum potassium) frequently accompanies alkalosis, the administration of supplemental potassium, in addition to ammonium chloride, may be indicated. Deficits of potassium may develop in the absence of alkalosis, especially when, in addition to the renal losses of potassium produced by mercury, the food intake is curtailed because of anorexia or extrarenal losses of potassium are produced by vomiting, diarrhea, or resins. Since potassium deficiency can produce necrosis of heart muscle as well as digitalis toxicity with serious arrhythmias, it should be diligently sought for and promptly corrected. The clinical evidences of potassium deficiency have been summarized in Table 2. If a deficit is present, 3 to 4 gm. of potassium chloride daily for several days will usually suffice to replenish body stores. For intravenous use, 4 gm. of potassium chloride can be dissolved in a liter of 5% glucose in water and injected

TABLE 4.—*Correction of Mercurial Refractoriness*

Cause	Correction
I. Hypochloremic alkalosis	A. Acidifying measures
	1. Ammonium chloride
	2. Acetazoleamide
	3. Ammonium chloride and acetazoleamide
	B. Potassium chloride
II. Potassium deficiency	Ingestion or injection of potassium salts
III. Low-salt syndrome	Hypertonic saline solution
A. Acute dilution hyponatremia	
B. Chronic dilution hyponatremia	
IV. Low glomerular filtration rate	A. Intravenous aminophylline
	B. Perhaps rest in bed or in a chair
V. Erect posture; exercise	Rest

|| References 24-26.

intravenously over a period not less than two and one-half hours. Potassium deficiency can often be prevented if about 2 gm. of potassium chloride are administered on the day of and the day following the injection of mercury. This is a safe procedure in patients who do not have severe renal insufficiency or oliguria.

pensation of the acidosis thus produced may increase the susceptibility to CO_2 narcosis.[27] Both respiratory acidosis and metabolic alkalosis are characterized by a high serum bicarbonate and low serum chloride; in both states the urine may be acid in reaction and contain increased amounts of ammonia and chloride. The salient points in differential

TABLE 5.—*Differential Diagnosis of Respiratory Acidosis and Metabolic Alkalosis in Patients with Congestive Heart Failure and Pulmonary Disease*

	Respiratory Acidosis	Metabolic Alkalosis
I. Cause	Alveolar underventilation at any given metabolic rate	Loss of fixed acid from, or accession of alkali to, the extracellular fluid; shrinkage of extracellular volume without loss of bicarbonate
II. Physiological derangement	A. Airway obstruction (obstructive ventilatory defect) Extensive emphysema with expiratory obstruction resulting from 1. Loss of lung elasticity, 2. inspissated secretions, or 3. bronchospasm B. Central respiratory depression (restrictive ventilatory defect)	A. Loss of acid into urine and into tissue cells associated with potassium deficiency B. Loss of edema without commensurate loss of sodium bicarbonate C. Gastrointestinal losses of acid—vomiting or gastric suction D. Excessively rapid administration of alkalinizing salts (e. g., $NaHCO_3$, Na lactate, etc.)
III. Clinical history	A. Emphysema with obstruction: prolonged history of exertional dyspnea, with comparatively mild orthopnea and atypical paroxysmal nocturnal dyspnea developing late; often, chronic cough with sputum B. Central respiratory depression: administration of central depressor drugs or C. N. S. disease (e. g., arteriosclerosis)	Exertional dyspnea usually associated with prominent orthopnea and paroxysmal nocturnal dyspnea
IV. Physical examination	A. Emphysema with obstruction: diminished breath sounds despite increased respiratory effort; tachypnea; expiratory wheezing; relatively fixed chest cage B. Central respiratory depression: diminished breath sounds with diminished respiratory effort; slow shallow respirations	Increased respiratory effort with breath sounds fairly well transmitted; tachypnea; fine rales
V. Chemical characteristics	Blood pH usually low; sometimes normal	Blood pH usually high; serum K sometimes low
VI. O_2 saturation and hematocrit value	A. Emphysema with obstruction: profoundly desaturated; polycythemia common B. Central respiratory depression: slightly or moderately desaturated; may be normal if stimulated	Usually only slightly desaturated; sometimes normal
VII. Response to 100% O_2	A. Emphysema with obstruction: sometimes irritability and nervousness; sometimes drowsiness or coma; usually a rise in serum bicarbonate and pH B. Central respiratory depression: variable response	No mental clouding or noteworthy chemical changes
VIII. Response to K	No response	Infrequently, correction of alkalosis

Many patients with heart failure suffer in addition from varying degrees of pulmonary disease. Severe pulmonary insufficiency may be associated with a respiratory acidosis which can not easily be distinguished from a metabolic alkalosis. The administration of large amounts of ammonium chloride to a patient with respiratory acidosis, in the mistaken impression that a metabolic alkalosis exists, may be hazardous, since the decom-

diagnosis are listed in Table 5. Usually, the clinical history of prolonged dyspnea without commensurate orthopnea or paroxysmal nocturnal dyspnea and the markedly diminished breath sounds on physical examination, with evidences of airway obstruction or ventilatory depression (such as may result from excessive amounts of sedative drugs, morphine, or cerebral arteriosclerosis) will suffice to distinguish respiratory acidosis

from metabolic alkalosis. A low blood pH, profoundly desaturated oxygen content of blood,[28] or a rise in serum bicarbonate following the administration of 100% oxygen by mask for one-half hour or more will definitely establish the diagnosis should clinical criteria prove ambiguous.

Hyponatremia with edema (low-salt syndrome) is a third cause of mercurial refractoriness. Chronic hyponatremia in patients with congestive heart failure is often accompanied by anorexia, lethargy, mental confusion, azotemia, and a tendency toward hypotension. The development of this state is not associated with acute losses of salt. Correction of the hyponatremia with hypertonic saline solution may increase the responsiveness to mercury.[29] However, more salt is usually required to raise the serum sodium to normal than is excreted in the urine. Moreover, the clinical picture usually does not improve after hypertonic saline solution.

Following paracentesis, repeated thoracenteses, or a massive mercurial diuresis, an acute dilution hyponatremia may develop, presumably because the marked losses of sodium chloride result in a shrinkage of the effective extracellular volume, which acts as a stimulus for both thirst and water retention. But the retention of water without salt will result in marked dilution of the body without replenishing the volume deficit. Hence, symptoms of both water intoxication (lethargy and mental clouding) and vascular insufficiency (hypotension and azotemia) tend to appear. The development of acute dilution hyponatremia is most likely to occur in those patients whose edema has largely disappeared with the diuresis or paracentesis or who had no salt retention to begin with.

To correct the hyponatremia, hypertonic saline solution—3% or 5%—should be given in amounts calculated from the product of the difference between the normal and depressed concentrations of sodium and the estimated volume of total body water.[30] If sodium determinations are not available, an approximation can be made by adding a factor of 10 to the sum of the concentrations of bicarbonate and chloride when these are expressed as milliequivalents per liter.[31] Such an approximation can only be made if there is no marked retention of fixed acids, such as occurs in renal failure, which will reduce the concentration of bicarbonate without necessarily altering the concentration of sodium or chloride. For example, to correct the hyponatremia of a 60 kg. man whose sodium is 125 mEq/L., the amount of hypertonic saline solution can be estimated in the following way:

$140 - 125 = 15$ mEq./L. (desired rise in serum sodium concentration)

$0.7 \times 60 = 42$ liters (volume of total body water)

$15 \times 42 = 632$ mEq. of sodium (amount necessary to raise the serum concentration to 140 mEq/L.)

632×58.5 (molecular weight of NaCl) $= 36{,}972$ mg., or about 37 gm.

This amount of salt is contained in 740 cc. of 5% saline solution. The salt should be given in several divided doses, with careful evaluation of the response before each injection. Water should be restricted on the days that hypertonic saline solution is given.

The low rate of glomerular filtration often seen in advanced heart failure is considered responsible for some instances of refractoriness. Elevation of the filtration rate with intravenous aminophylline (0.48 to 0.72 gm.) may restore responsiveness to mercury.[29] If this measure is employed, care should be taken to inject aminophylline slowly about one to two hours after the injection of mercury, when a peak mercurial effect may be anticipated.

Finally, it should be emphasized that the erect posture and exercise enhance the renal retention of salt in cardiac patients, much as they do in normal subjects. By removing this stimulus to sodium retention, a satisfactory diuretic response to mercury may be facilitated.

In Table 4, the treatment of mercurial refractoriness is summarized.

Ammonium Chloride.—Ammonium chloride is the principal acidifying salt used in

the treatment of edema. The ammonium ion is converted to urea in the liver, with hydrochloric acid being formed in the process. The hydrochloric acid thus formed decomposes bicarbonate, tending to produce a high-chloride acidosis. In normal subjects the kidneys respond by excreting principally sodium and potassium with the chloride during the first several days; thereafter, chloride is excreted mainly with ammonium. Ammonium chloride has been used for three purposes in edematous patients: to promote salt loss, to potentiate mercurial diuresis, and to correct alkalosis.

As an agent to promote sodium loss, ammonium chloride is usually ineffective in severe congestive failure. In contrast to its action in normal subjects, the tenacious sodium retention so characteristic of the congestive state prevents this cation from being excreted into the urine despite large doses of ammonium chloride (up to 10 gm. daily), even in the early phases of ammonium chloride administration.[32] Instead, potassium excretion is accelerated, leading to hypokalemia. In addition, acid excretion by the kidneys rises more slowly than in normal subjects, leading to a more severe degree of systemic acidosis even when renal disease is absent. If the capacity of the kidneys to excrete acid is compromised by the presence of renal disease as well, a severe high-chloride acidosis may result, producing stupor, hyperventilation, and azotemia. In addition to the dangers of potassium deficiency and acidosis, large doses of ammonium chloride can provoke anorexia, nausea, vomiting, and diarrhea. For these reasons, it is doubtful whether ammonium chloride is of any value as a diuretic in heart failure.

The principal function of ammonium chloride in heart failure is its use in conjunction with mercurial diuretics. Given in modest doses (2 to 5 gm. daily) the day before and for two days after the injection of mercury, it can greatly enhance sodium excretion, at the same time tending to prevent the development of alkalosis. The mechanism whereby ammonium chloride potentiates mercurial action is not clear; it is apparently independent of any alteration in plasma acid-base balance.¶ If alkalosis develops with mercurial diuretics, this can be corrected by the oral or intravenous administration of ammonium chloride, with a restoration of responsiveness to subsequent mercurial injections.

The administration of ammonium chloride, particularly in patients with renal disease, should be accompanied by determinations of serum bicarbonate and chloride. If serious liver disease is also present, the acid should be given cautiously because of the danger of ammonium intoxication.[35] Finally, in patients with primary pulmonary insufficiency, respiratory acidosis should be clearly distinguished from hypochloremic alkalosis,

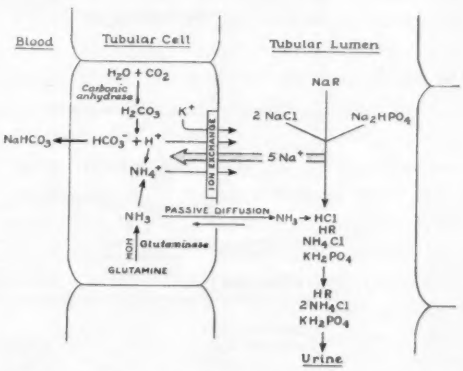

Fig. 1.—The role of carbonic anhydrase and glutaminase in the renal excretion of acid.

since the mistaken administration of ammonium chloride to patients with primary carbon dioxide retention can result in a severe decompensation of their acidosis, and perhaps thereby increase the likelihood of carbon dioxide narcosis.

Acetazoleamide.—Acetazoleamide is a potent relatively nontoxic inhibitor of the enzyme carbonic anhydrase. All the renal effects of acetazoleamide appear to be a result of its capacity to block the tubular secretion of hydrogen. Normally, some of the sodium reaching the distal tubule of the kidney is reabsorbed in exchange for both potassium and hydrogen.[36] The chief source

¶ References 33 and 34.

of hydrogen is the ionization of carbonic acid formed by the hydration of CO_2 under the influence of carbonic anhydrase.[37] These processes are illustrated in the model cell in Figure 1. When the action of carbonic anhydrase is inhibited with acetazoleamide, the secretion of acid in exchange for tubular sodium is impaired. Increased amounts of sodium exchange for potassium, thereby accelerating potassium excretion. Sodium excretion into the urine is also enhanced, presumably because the accelerated reabsorption of sodium for potassium is not sufficient to compensate for the blocked exchange of sodium for hydrogen. Since the bicarbonate of the tubular fluid is no longer decomposed by acid, increased amounts appear in the urine, rendering it alkaline. The net effect of these reactions is the formation of an alkaline urine, containing greater quantities of bicarbonate, sodium, potassium, and water, and the development in the serum of a high-chloride acidosis with or without hypokalemia. # Although mild hyperchloremic acidosis persists in normal subjects and some patients with heart failure, the composition of the urine returns to a normal pattern after prolonged administration of the drug. This is not the result of an inactivation of acetazoleamide, since the analysis of rat kidneys for carbonic anhydrase activity reveals the same degree of inhibition after 14 days of continuous treatment as can be demonstrated initially.* Rather, the restoration of a normal urine composition, despite continuous acetazoleamide administration, is probably a consequence of the activation of renal glutaminase and perhaps other ammonia-producing enzyme systems.[42] Both increased ammonia and hydrogen production can result from glutaminase adaptation, since the hydrolysis of glutamine yields not only

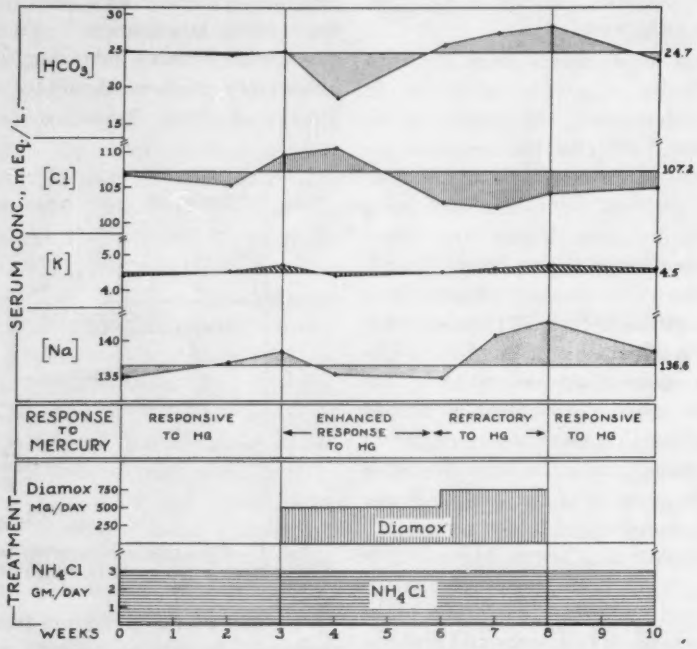

Fig. 2.—Effect of chronic acetazoleamide administration on serum bicarbonate and mercurial responsiveness in congestive heart failure.

References 38-41.

* Seldin, D. W., and Rector, F. C., Jr.: Unpublished data.

ammonia but a new carboxyl group which is completely ionized at physiological pH and can donate hydrogen to the over-all reaction. In this manner, the effects of carbonic anhydrase inhibition can be largely compensated.

Because it accelerates sodium excretion and tends to produce hyperchloremic acidosis, acetazoleamide has been used both as a diuretic and as a means of potentiating mercurial action. Except in cor pulmonale, acetazoleamide has proved to be only mildly effective.† Usually a modest initial diuretic response can be elicited, but continuous administration usually fails to elicit further significant sodium loss. This may be a result of the effects of the activation of glutaminase described above. As a mild diuretic it can be given in single doses of 250 mg. a day. Larger amounts appear no more effective. On theoretical grounds it appears likely that with long intervals between acetazoleamide administration (more than two days ‡) resistance to the drug might be averted, since activation of compensatory mechanisms would be less apt to occur. Moreover, the low bicarbonate level, which has been considered a factor in resistance, might be regenerated, in the intervals between drug administration, by the excretion of ammonium chloride.[40]

Since it tends to produce a high-chloride acidosis, acetazoleamide can be used to potentiate mercurial diuretics. This effect can be enhanced by the simultaneous administration of ammonium chloride in small amounts. Here, too, however, acetazoleamide should not be given continuously. In Figure 2 the effects of chronic acetazoleamide and ammonium chloride administration on serum electrolytes and mercurial responsiveness are illustrated. § The initial administration of acetazoleamide was accompanied by a mild diuresis and enhanced mercurial responsiveness. At this time a hyperchloremic acidosis had developed. After three to four weeks of continuous administration, the serum bicarbonate slightly exceeded control values despite the continued administration of ammonium chloride. With the discontinuance of acetazoleamide, serum bicarbonate fell and mercurial responsiveness reappeared. The rise in bicarbonate from initially depressed levels despite continued acetazoleamide administration emphasizes the need for intermittent administration, with prolonged periods without the drug.

Moreover, acetazoleamide appears to inhibit the diuretic effect of mercury, even during the early stages of the administration of this drug and ammoninum chloride, despite the development in the serum of a high-chloride acidosis. However, if acetazoleamide is discontinued shortly before mercury is given, the setting of hyperchloremic acidosis produced by preparatory administration of acid and carbonic anhydrase inhibitor results in a correction of mercurial unresponsiveness and satisfactory diuresis.[44] Since acetazoleamide, like ammonium chloride, tends disproportionately to accelerate potassium rather than sodium excretion in severe refractory heart failure, patients receiving these agents in combination should be carefully scrutinized for evidences of potassium deficiency.

COMMENT

These remarks, emphasizing as they do certain complications of diuretic measures, are not intended necessarily to discourage their use or to minimize their value. Rather, by appreciation of the deleterious potentialities of certain diuretic agents, untoward effects can often be prevented, complications can be anticipated and promptly corrected, and more effective diuresis can be achieved.

† References 40, 41, and 43.

‡ References 40 and 41.

§ Seldin, D. W., and Harris, A. W.: Unpublished data.

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Corticoid Therapy in Eye Diseases

Sustained Restoration of Vision in Certain Eye Diseases Considered Corticoid-Refractory or Clinically Irreversible

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By early 1950, short-term corticotropin treatment at modest dosage levels was shown to give only incomplete or transient improvement in the more serious acute disorders of the posterior ocular segment or optic nerve, while, in more chronic eye diseases, it seldom gave any significant relief. In an attempt to improve upon these results, we began a study of the response to intensive long-acting corticotropin treatment, fully individualized both in dosage and duration of therapy. Originally, there were envisioned only trials in patients with those acute eye diseases which had been reported to respond unsatisfactorily to hormonal treatment. However, as the study progressed, it occasionally became necessary to treat a patient who presented suitable acute lesions in one eye and older, apparently inactive, clinically irreversible lesions in the other eye as a result of previous attacks of the same illness. In several such patients, the first of whom is illustrated by Figure 1, we noted that, usually toward the close of treatment of the acute disorder, substantial improvement had occurred in the older lesions and that this benefit was sustained after treatment ended. After several similar observations, the study was broadened to include a group of patients who showed only long-standing chronic eye disease.

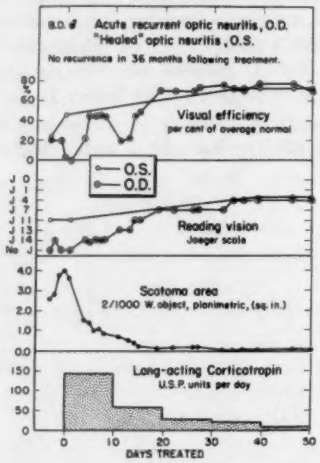

Fig. 1.—Improvement in 'healed," "inactive" optic neuritis O. S. during treatment of acute optic neuritis O. D.

This report summarizes observations on both the acute and chronic eye disease groups

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From The Unit for Metabolic Research, Department of Medicine and the Department of Ophthalmology, Wayne University College of Medicine and City of Detroit Receiving Hospital, and the Rackham Arthritis Research Unit, Department of Internal Medicine and the Department of Ophthalmic Surgery, University of Michigan Medical School. Director, The Unit for Metabolic Research, and Armour Fellow in Quantitative Human Pharmacology and Therapeutics, Department of Medicine, Wayne University College of Medicine and City of Detroit Receiving Hospital (Dr. Wolfson); Instructor in Ophthalmic Surgery, University of Michigan Medical School; Instructor in Ophthalmology, Wayne University College of Medicine (Dr. Quinn); Instructor in Ophthalmology, Wayne University College of Medicine (Dr. Spearman).

through April, 1954. Preliminary reports of these findings have been published elsewhere.* Present recommendations for practical therapy will be summarized briefly after the results are discussed.

*Average Data on Therapeutic Response and Corticotropin Dosage in Eye Patients**

	Less Severe Acute Disease	More Severe Acute Disease	Chronic Disease
Maximum Improvement Achieved at Any Time During Treatment, %			
Satisfactory result			
Excellent response	100	69	39
Good response	0	11	39
Total	100	79	78
Unsatisfactory result			
Fair response	0	0	11
Poor response	0	21	11
Total	0	21	22
Status at Present or at Last Visit, %			
Full improvement maintained			
Without therapy	90	53	16
On maintenance therapy	10	26	56
Total	100	79	72
Average follow-up in patients off therapy, mo.	18	21	8
Average Long-Acting Corticotropin Dosage Data			
Duration of therapy, days	64	199	452
Total corticotropin, units	2,228	6,166	15,400
Maximum daily dose, any consecutive 10 days, units/day	68	131	161
Average daily dose, first 100 days, units/day	41	62	73
Average daily dose after first 100 days, units/day	..	..	26

* Through the use of correction factors given elsewhere,[3] all cortocotropin dosages are expressed in terms of a single daily dose of long-acting corticotropin in heavy gelatin.

Twenty-one patients considered to have less severe acute eye disease included those with anterior uveitis, recurrent, which had been demonstrated refractory to topical cortisone (8); central angiospastic retinopathy (3), and retrobulbar neuritis (7 of unknown etiology, 3 associated with multiple sclerosis).

Eighteen patients considered to have more severe acute eye disease included those with total blindness due to the binocular retrobulbar neuritis of Devic's neuromyelitis optica (1), acute chorioretinitis and posterior uveitis (11), and acute optic neuritis (7).

Thirty-six patients with chronic eye disease included patients with anterior uveitis refractory to topical cortisone (2 of unknown etiology, 2 associated with rheumatoid arthritis, 1 due to sarcoidosis), disseminated chorioretinitis (16), retrobulbar neuritis (2 due to syphilis, 4 associated with multiple sclerosis, and 2 of unknown etiology), and single patients with each of the following syndromes: episcleritis, Mooren's ulcer, diffuse retinitis with periphlebitis, Coats' retinitis exudativa, retinitis pigmentosa, retinitis circinata, and central angiospastic retinopathy.

When a patient was treated for less than 100 days, the average dose for the entire treatment period is given under the heading "average daily dose, first 100 days." In the case of acute eye disease, there are insufficient data to warrant calculation of an average dose for treatment over 100 days in length.

* References 1-4.

OVER-ALL RESPONSE IN ACUTE EYE DISEASE

The Table summarizes the therapeutic response in acute eye disease. The disorders studied are grouped into two categories, mild and severe, because our earlier findings had shown these two categories to be characterized by log dose/response relationships which had little or no overlap. The category of milder acute eye disease includes acute retrobulbar neuritis, acute central angiospastic retinopathy, and acute recurrent iridocyclitis demonstrated refractory to topical cortisone, that is, chiefly disorders with a serous inflammatory or functional vasomotor pathology. The category of more severe acute eye disease includes those which are characterized by hemorrhagic, granulomatous, or necrotizing processes.

Twenty-one patients with acute disorders of the milder types were treated for an average 64 days with a mean 2228 units of long-acting corticotropin. On the average, the maximum dose needed for any consecutive 10-day period was 68 units per day. Restoration of normal vision was achieved in all patients during treatment and was maintained thereafter. Withdrawal of therapy was successfully accomplished without relapse in 19 patients, although occasionally the first trial failed and a second or a third trial, often with the aid of pyrogen, was necessary. The other two patients required maintenance treatment not because of their eye disease but for extraocular corticoid-sensitive disorders. The 19 patients in whom treatment was discontinued have maintained their full improvement during an average 28-month follow-up period, except that it has been necessary to treat one woman for an attack of acute retrobulbar neuritis (due to multiple sclerosis) in the eye which was not involved in her original episode.

In the patients with acute disorders in the more severe category, it was necessary to give more intensive and more prolonged treatment and, on the whole, the therapeutic response was somewhat less satisfactory. Nineteen patients received an average 199 days therapy with a total of 6166 units of

long-acting corticotropin. The maximum dose used in any consecutive 10 days averaged 131 units per day. Fifteen of the 19 patients (79%) recovered normal or useful vision during treatment and have maintained their full improvement without subsequent relapse. In 5 of these 15 recovered patients, maintenance treatment has been found necessary, either because of continuing activity of the eye disease or because of an extraocular corticoid-sensitive systemic disorder. In the 10 patients from whom treatment was withdrawn successfully, an average 31-month follow-up period has been passed without relapse.

The improved results in reportedly hormone-unresponsive acute eye disease seem to have been due chiefly to an increase in the intensity and duration of therapy and, to a smaller extent, to liberal use of maintenance therapy when it seemed necessary. It is important to remember that the numerical figures just cited are average values and that the range of variation is very large, particularly in patients with the more severe acute disorders. An occasional patient has required the equivalent of a single daily dose of 480 units of long-acting corticotropin (i. e. 60 units intramuscularly every six hours [3]) for more than 10 consecutive days.[3]

OVER-ALL RESPONSE IN CHRONIC EYE DISEASE

The Table also summarizes average data on 36 patients treated for chronic eye disease, including 7 with chronic anterior segment or scleral disorders, 16 with disseminated chorioretinitis, 5 with other inflammatory or degenerative retinal disorders, and 8 with chronic retrobulbar neuritis, which was of unknown etiology in 2 instances, associated with multiple sclerosis in 4 instances, and due to syphilis in 2 instances.† Through April 1, 1954, the average patient had been treated for 452 days with a total of 15,400 units of long-acting corticotropin. The average patient required 161 units per day of hormone for at least one 10-day period. In well over half of the patients, this period of maximum dosage occurred during the first 100 treatment-days. The average daily dosage given during the first 100 days of treatment was 73 units per day, but after the first 100 days an average daily dosage of 26 units per day was sufficient.

The decrease in dosage requirements after the first 100 treatment days is no doubt partly due to the increased responsiveness of the previously stimulated adrenal cortex, which, in a few patients, may be striking in degree, as will be illustrated later. That other factors are even more important is suggested by the observation that this dosage decrease was much more marked in patients who enjoyed good physical health except for their localized eye disease than it was in patients whose chronic eye disease was a manifestation of some systemic disorder such as rheumatoid arthritis or sarcoidosis.

A number of investigators have noted that normal adults given corticotropin, cortisone, of hydrocortisone show considerably less marked hypercorticoid symptoms than do systemically ill patients given equal dosages (except perhaps in the very first days of their treatment) and that, in turn, the adrenalectomized person is much more sensitive to corticoid dosage than is the systemically ill patient. In our first report,[1] we noted an impression that patients in good health except for localized eye disease were relatively resistant to symptomatic hypercorticism. This impression has been reinforced by subsequent experience, and it seems likely that, like the physically healthy adult, patients with only localized eye disease are relatively refractory both to such "favorable" effects of the hypercorticoid state as the improvement in mood and to its more dangerous manifestations. In the entire group of 75 patients treated for acute or chronic eye disease, hypercorticoid manifestations required termination of therapy in

† "Chronic retrobulbar neuritis" has seemed a more satisfactory term than "primary optic atrophy," since it avoids the implication that the characteristic pale white optic disc is due to nerve atrophy rather than to ischemia. The latter term requires the assumption that nerve regeneration has occurred when such patients show marked improvement.

only six patients. One patient, whose mother had clinical diabetes mellitus, developed steroid diabetes and, while receiving 80 units per day of corticotropin and 160 units per day of NPH insulin, continuously excreted between 150 and 250 gm. of glucose per day, without significant ketonuria. Her eye condition was controlled by intravitreous hydrocortisone, and parenteral treatment was withdrawn. She became normoglycemic and aglycosuric about one month later. Treatment was withdrawn from one other patient because of edema and hypertension which could not be controlled medically and from the remaining four patients because of heightening of preexistent neurotic anxiety. The development of absolute refractoriness to intramuscular purified corticotropin (ACTX-corticotropin, corticotropin A) of porcine origin has not been observed, but two patients became relatively unresponsive to this material. In one, the unresponsiveness was rapidly corrected by transferring the patient to similar material of bovine origin; in the other, this did not restore normal responsiveness but the addition of equine pituitary adrenal weight factor, supplied by Dr. Arthur Rinfret, was effective.

In 28 of the 36 patients with chronic eye disease, 78% of those treated, useful or normal vision was restored during treatment, but the full improvement was not maintained in 2 patients. One, a young man with chronic anterior uveitis due to sarcoidosis, responded inadequately until systemic treatment was reinforced by biweekly instillation of hydrocortisone into the anterior chamber of each eye. A second young man, with Coats' disease (retinitis exudativa), lost useful vision when, after having regained 20/20 central acuity, he discontinued therapy, against advice. The remaining 74% (26 of the 36 patients treated) have maintained their full improvement for an average of 20 months as of April 1, 1954. In most cases, maintenance of improvement has required continuous therapy, though at reduced dosages.

Figure 2 shows the improvement in central visual acuity and in reading vision observed in individual patients. (This Figure does not include all patients treated for chronic eye disease, since in some conditions these parameters are not as good indices of status as are other measurements, such as slit-lamp findings.) Figure 2 suggests that few patients fail to obtain some benefit from treatment, although the degree of improvement may be insufficient to be considered restoration of useful vision. It also implies that, in a rough way, the outcome of therapy is better in those patients whose vision is better preserved before treatment is given.

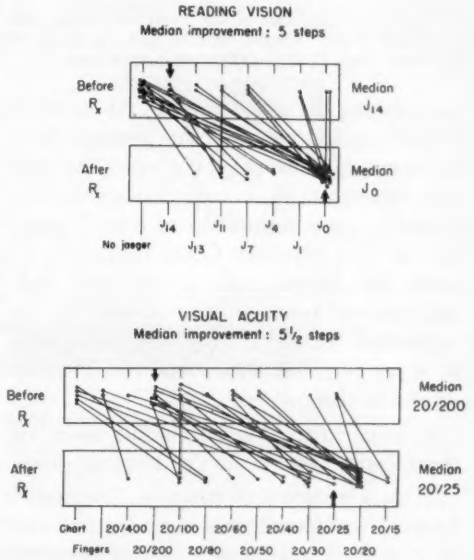

Fig. 2.—The extent of improvement in central visual acuity and in reading vision noted in individual patients during treatment for chronic eye disease.

QUALITATIVE FEATURES OF THE THERAPEUTIC RESPONSE IN CHRONIC DISORDERS OF THE OPTIC NERVE OR RETINA

Five unusual features of the response of these patients require further discussion:

1. In a particular patient with a given disorder, the outcome of treatment usually cannot be predicted from ophthalmoscopic or other pretreatment findings. There are certain exceptions to this statement. If a patient has a parafoveal scotoma and reduced foveal vision attributable principally to edema

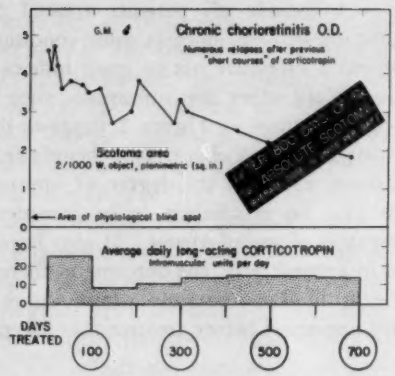

Fig. 3.—An instance of the extremely slow rate at which some chronic retinal and optic nerve lesions recover during corticotropin treatment.

surrounding the lesion causing the scotoma, a highly satisfactory outcome generally may be expected. Conversely, if a lesion has damaged the macula so severely that white sclera is visible, good restoration of central acuity has not been obtained. Other supposedly irreversible changes, such as the pale white optic disc of primary optic atrophy or the pigmented lesions of chronic corioretinitis, have not been found to preclude a good response to therapy.

2. Even in the most favorable cases, the therapeutic response always develops slowly.

3. In a minority of patients, "therapeutic latency" is observed; that is, no improvement is seen until treatment has been given for one or more months. Recovery may then begin at dosages considerably below those employed somewhat earlier.

4. Once a given level of improvement is obtained it generally may be sustained by treatment much less intensive than was required for its initial emergence.

5. Substantial improvement has been seen in disorders usually classed as "degenerative" as well as in those considered to be "inflammatory." A number of these features are illustrated in the following case reports.

Figure 3 emphasizes the slow rate at which improvement may occur and the prolonged period of treatment which may be required before the best improvement is obtained. In this patient with chronic chorioretinitis only observational periods measured in hundreds of days were adequate to reveal progressive improvement; an untrained observer might well have considered that no improvement was occurring. This patient well illustrates the striking increase in adrenocortical responsiveness to corticotropin sometimes observed during therapy. His 24-hour excretion of corticoids while receiving 11 units per day of corticotropin at about Day 800 was over 60 mg. per 24 hours (as neutral butanol-extractable Porter-Silber chromogen). Between the 800th and 900th treatment day, he then manifested such a marked increase in response that it became necessary to reduce his daily dosage to 2 units per day of corticotropin. On this dosage, his eosinophile count each morning before his daily injection was between 150 and 250 cells per cu. mm., while each afternoon, eight hours after his daily 2 units, the count fell to between 0 and 20 cells per cu. mm., a response identical to that earlier produced by 11 units per day of corticotropin and one which, in a normal subject, would have required the administration of 60 to 100 units of corticotropin. It is thus possible to estimate that his adrenal cortex responsiveness to corticotropin was, roughly, 30 to 50 times that of a normal adult.

Figure 4 emphasizes both the slow rate of improvement and the necessity for the use of high dosages of corticotropin to initiate

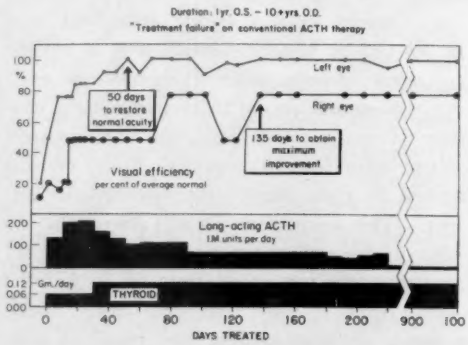

Fig. 4.—Successful individualized corticotropin treatment of a 1-year-old, supposedly "corticotropin-refractory," chronic chorioretinitis in a patient's left eye and of a 30-year-old, "clinically irreversible," apparently inactive chronic chorioretinitis in his right eye.

improvement in certain patients. This man, who had chorioretinitis of 1 year's duration O. S. and of 30 years' duration O. D., had received brief corticotropin treatment elsewhere, and, because he did not even show transient improvement, was stated to be hormone-refractory. In response to adequate binocular vision was regained. This patient's subsequent course illustrates the small maintenance requirements of some patients after recovery. For over two years, his essentially complete remission has been maintained by single weekly doses of 80 units of long-acting corticotropin.

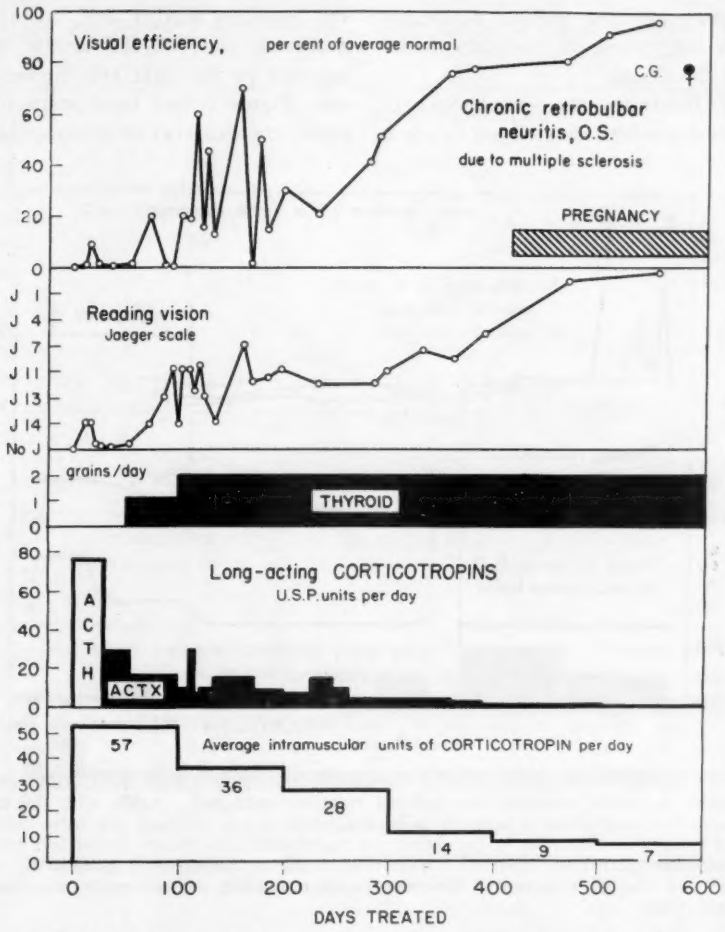

Fig. 5.—"Therapeutic latency" during the "delayed therapocorticoid effect"; the recovery of normal vision by a patient with chronic retrobulbar neuritis due to multiple sclerosis, in whom the eventual outcome of therapy was not predictable after 200 days of treatment.

dosage, 20/20 vision was restored to his left eye by Day 50 and 20/50 acuity was regained in the right eye by Day 135. Somewhat later it became impossible to demonstrate parafoveal scotomata in either eye, even to the 1/1000 white object. Eventually, after a brief period of annoying diplopia, normal

Figure 5 suggests how difficult it may be to estimate the final degree of functional restitution even after there has been some indication of improvement. These data, from a patient with chronic retrobulbar neuritis due to multiple sclerosis, suggested that some improvement had occurred by the 200th

treatment day, but, at this time, they gave no indication of the eventual restoration of entirely normal vision which was to follow. This patient went through a normal pregnancy between the 400th and 670th treatment days. In her, and in three other women who went through pregnancy during prolonged corticotropin treatment, the continuous use of this hormone has been without noticeable effect upon the course of pregnancy, the delivery, or the infant.

Figure 6 illustrates the extraordinarily prolonged period which may elapse before a therapeutic response is obtained. About three years ago, we were unsuccessful in a vigorously conducted attempt to reverse severe acute central chorioretinitis in a young woman whose left eye already had been seriously impaired by several earlier attacks of the same disease. In her right eye, treatment only produced some diminution in size of her very large central scotoma to all objects and to light. However, long-term administration of corticotropin was continued because the older lesions of her left eye showed worthwhile improvement, from 20/200 acuity before treatment to 20/80 in its earlier phases and gradually thereafter to 20/45 at present. After two years of continuous treatment it became clear that the area of the dense central scotoma in the right eye was becoming smaller, and, during the third treatment year, 20/100 acuity was finally regained in the right eye. Somewhat later, after Figure 6 had been prepared, she reported the existence of a transparent area in the center of the previously opaque scotoma in her right eye, and, as an objective correlate of this change, she became able to read portions of the 20/20 line of the Snellen chart. (At this time she was able to read the entire 20/80 line without error.) This restoration and maintenance of 20/45 and 20/80 vision in the eyes of a young woman apparently certainly doomed to complete loss of central acuity illustrates why we consider it

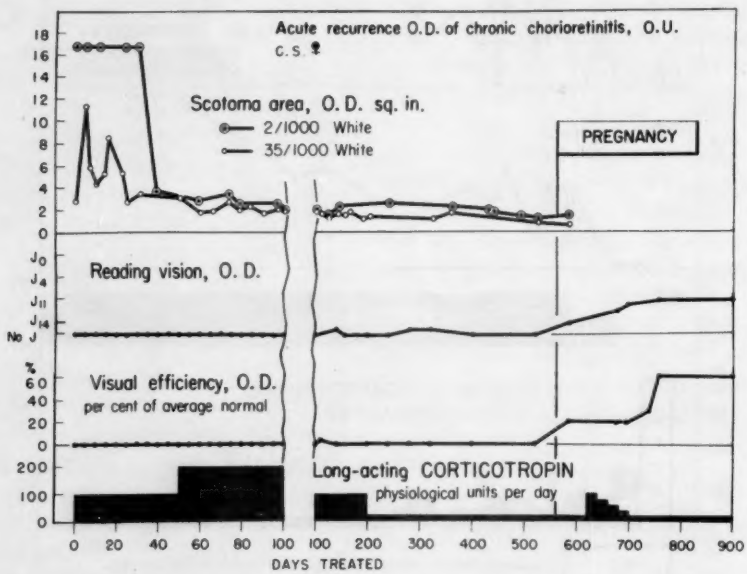

Fig. 6.—The most prolonged period of "therapeutic latency" so far observed. Although beginning return of central vision in the patient's right eye coincided roughly with the onset of pregnancy, this congruence is believed to be accidental, since, at about the same time, there occurred a significant increase in the activity of the chorioretinal lesions in her left eye which necessitated the period of increased dosage shown. Since, during early pregnancy, one eye improved and the other showed a flare-up, in all probability neither event was related to the pregnant state.

impossible to stipulate any fixed period of therapeutic trial which will be completely adequate for all patients.

Figure 7 illustrates the therapeutic reversal of retinitis pigmentosa, a "degenerative" disorder. The data are from a 40-year-old Negro woman with typical long-standing progressive retinitis pigmentosa, night blindness, and sufficient field constriction to produce typical "gun-barrel vision." The early improvement in central acuity during treatment may be considered mere relief of secondary macular edema rather than true reversal of the primary disorder. However, after she had been treated for approximately 300 days, fundamental improvement in the causative lesion was demonstrated by widening visual fields and relief of night blindness.

An unintentional clinical experiment showed that this improvement in retinitis pigmentosa was not accidental. During the Spring of 1954, the patient was supplied with long-acting corticotropin from a lot which was subsequently found to have lost over two-thirds of its original potency when stored at room temperature. Within the month after she began use of this material, there occurred a severe relapse, which was promptly reversed by treating her in the hospital for one week with corticotropin known to be fully effective by human bioassay.

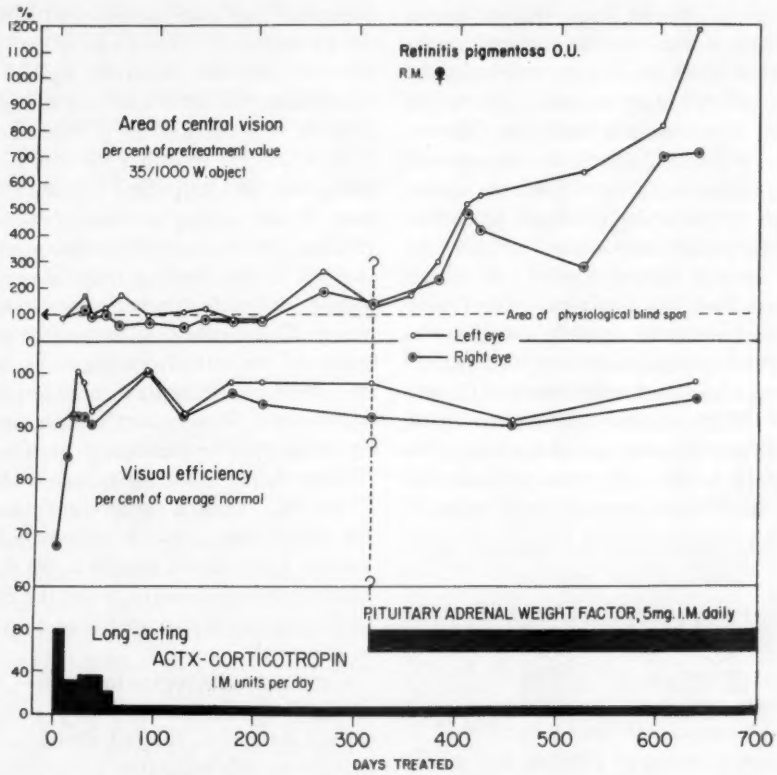

Fig. 7.—Unusually prolonged "therapeutic latency" during successful corticotropin treatment of a chronic "degenerative" eye disease, retinitis pigmentosa.

The course of hormonally induced recovery in chronic optic nerve and retinal disorders is a unique phenomenon, which has no parallel in any other group of disorders for which corticotropin is effective. The extent of functional restoration, as well, fre-

quently exceeds that which can be explained under current concepts of the potential reparability of these ocular structures of neuroectodermal origin. Restoration of function in such "degenerative" disorders as retinitis pigmentosa, Leber's hereditary optic atrophy,‡ the Kuhnt-Junius type of macular retinopathy, the retinal degeneration of high myopia, and Coats' disease together with the frequent occurrence of a period of "therapeutic latency" before improvement begins clearly implies that recovery depends upon some action other than mere supression of a chronic inflammatory process. The entire pattern of response is actually so different from known corticoid effects that it may well represent a new modality of corticoid action, for which we have suggested the term "delayed therapocorticoid effect." While increased adrenal cortex activity of critical degree sustained for a minimum critical duration appears to be an absolute essential, the "delayed therapocorticoid effect" has not yet been proved to depend only upon the 11-oxygenated 17,21-dihydroxy-20-ketocorticoids, since cortisone has not given equivalent results in our hands and hydrocortisone has received insufficient study for evaluation.

GENERAL PRINCIPLES OF THERAPY IN CHRONIC EYE DISEASE

The procedure recommended attempts to take into consideration those features of the unique response to corticotropin therapy which have just been described. Only the general philosophy of management will be given, since selection of patients, therapeutic criteria, pharmacology of long-acting corticotropin preparations, and adjunct precautions are amply described elsewhere.§

Long-acting corticotropin is ordinarily employed for treatment. Oral cortisone or hydrocortisone are less satisfactory both because of the reasons cited above and because either will certainly induce adrenal atrophy if given in the necessary doses for the period required. When daily administration of injections is absolutely impossible, a regimen which combines daily use of oral hydrocortisone with weekly injections of long-acting corticotropin will avoid this adrenal atrophy,‖ but its therapeutic efficacy has not been fully studied.

It is ordinarily unnecessary to hospitalize patients during the initial phases of treatment or, indeed, at any time, except occasionally when dosage is approaching maximum tolerance and it seems desirable to have the patient under close observation or to insure the absolute minimum sodium intake, which almost never is achieved in ambulatory patients. On the first day of treatment, blood is drawn in the morning for a basal eosinophile count and the patient is given a 100-unit dose of long-acting corticotropin intramuscularly. His eosinopenic response either six or eight hours after this initial dose provides a crude index of adrenal cortex responsiveness.¶ Daily doses of 80 to 199 units are given on the next following days, provided that there occurs neither rapid improvement in the eye disease nor intense subjective or objective hypercorticoid manifestations. Should either occur, dosage is reduced by 25 to 50%. Once a suitable daily dosage for the initial period has been selected in this way, it is continued for 10 to 30 days (depending on disease activity and the chronicity of the lesions) if no evidence of improvement is observed.

Once a patient begins to improve, however slowly,# no further arbitrary increases in dosage are made. Instead, thereafter, dosage is continuously regulated to that level which permits a slow but progressive improvement. That is, arbitrary dosage adjustment by rule

‡ Kuhn, H. S.: Personal communication to the authors.

§ References 1-4.

‖ References 4 and 5.

¶ References 3 and 4.

A common error among inexperienced therapists has been an attempt to accelerate improvement by increasing dosage. This will result in the appearance of undesirable hypercorticoid manifestations but usually does not increase the rate of recovery. In general, if a patient reports subjective improvement which cannot be verified immediately by objective testing, it is much better to defer an increase in dosage than it is to assume that the subjective impression was incorrect.

is replaced by the adjustment of dosage according to objective status. Once maximum improvement is attained, a process which may require from three months to more than two years, dosage is very gradually tapered down, both by decreasing the size of individual doses to a minimum of 40 to 80 units per dose and also by increasing the interval between doses, usually to a maximum of one dose per week. Complete withdrawal of treatment from successfully treated patients is deemed inadvisable, since our early experience indicated that, when this was done, retreatment was often necessary within six months. Present practice is to continue such patients on a single dose of 40 to 80 units of long-acting corticotropin given once each week.

When a patient has shown no improvement after he has received the initially selected dosage for 10 to 30 days, his dosage is increased gradually in steps of 20 to 40 units, the effect of each dose increment being observed for from 10 to 30 days before an additional increase is made. This process is continued until the advent of hypercorticoid symptoms indicates that the maximum dosage tolerated safely has been reached. If this peak dosage does not result in improvement after it has been continued for a prudent period, the daily dosage is reduced to the maximum level tolerated with relative comfort and is continued at this level for as long a period as appears indicated. The precise length of such a trial cannot be given in absolute terms, since, as the treatment period is extended, a decreasing but still significant number of patients will gradually come into remission. In each case, therefore, the final decision inevitably must depend on personal considerations. Clearly, it is more appropriate to give a prolonged trial to a patient with severe impairment of vision in both eyes than to a patient who has one entirely normal eye. In the latter event, one can be relatively certain that, should the well eye become acutely involved, the process may be effectively reversed by immediate and vigorous treatment.

GENERAL PRINCIPLES OF THERAPY IN ACUTE EYE DISEASE

Except in acute chorioretinitis and acute optic neuritis, the initial dosages and successive increments are the same as those employed for chronic eye disease, the major modification being that dosage elevations are made every four days if patients do not respond. Patients with acute chorioretinitis and acute optic neuritis receive more vigorous initial treatment because of the rapidity with which irreversible damage may develop. These patients should be hospitalized, given 100 units of long-acting corticotropin immediately, and, once their six- or eight-hour eosinopenic response has been studied, should be continued on 40 units of long-acting corticotropin every six hours. Sooner or later this high dosage will inevitably produce severe hypercorticism in most patients, and, to avoid this, patients must be watched carefully and dosage reduced by 50% once the first signs of beginning improvement are noted. It appears inadvisable to permit the customary delay in treating acute chorioretinitis until studies have been made for tuberculosis. The rare true tuberculous chorioretinitis which is an episode in miliary tuberculosis is usually easily recognizable and quite different in characteristics from typical acute disseminated chorioretinitis of unknown etiology. Patients in the latter category may receive chemotherapy prophylactically with hormonal treatment until their x-rays, tuberculin tests, and other procedures have been evaluated.

When patients with acute eye disease fail to show beginning improvement at maximum tolerated dosage, it is unlikely that they will do so at lower dosages, and discontinuation of treatment or additional measures such as intra-aqueous or intravitreous administration of hydrocortisone must be considered seriously. When they do improve, as in chronic eye disease, dosage is regulated to produce a slow but continuous improvement until full recovery is obtained, and then it is gradually tapered off, with the expectation that discontinuation of treatment will almost always

be possible. Occasionally, this will require more than one trial, and, if a second or third trial is necessary, the use of pyrogen to assist withdrawal [4] has been found very helpful.

SUMMARY

In certain acute disorders of the eye which have been reported to respond irregularly, incompletely, or transiently to hormonal therapy and in certain inflammatory and degenerative disorders of the eye reported not to show even an incomplete response to such treatment, intensive individualized long-term corticotropin therapy has permitted a majority of patients to regain normal or useful vision and, in almost all cases, to maintain their full improvement indefinitely thereafter.

Certain features of the therapeutic response in chronic disorders of the optic nerve or retina are unique to this group of disorders. They suggest that, in these cases, recovery may depend upon previously unknown actions of the hormones of the adrenal cortex.

The larger portion of the long-acting corticotropin used in these studies was H. P. Acthar Gel, Armour, or purified corticotropin-gel, Wilson, donated by the respective manufacturers. Corticotropin, cortisone, and hydrocortisone for these investigations also were received from Eli Lilly & Company; Merck & Company, Inc.; National Drug Company; Nordic Biochemicals Ltd.; Organon, Inc.; Parke, Davis & Company; G. D. Searle & Co.; The Upjohn Company, and Victory Packing Company.

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Adrenocortical Function During Long-Term Cortisone Therapy

Further Observations

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It has been demonstrated that treatment with cortisone causes suppression of adrenocortical function.* Further studies have shown that this suppression may be reversed by the administration of corticotropin even though the maintenance dose of cortisone is continued.[2]

The patients in this group have been studied at approximately yearly intervals since the initiation of their continuous therapy with cortisone. An earlier examination was reported previously.[2] The present study comprises the results of investigations which were made in 1953 and 1954 to determine whether the adrenal cortex would still respond to corticotropin and also to observe the effect of long-term therapy with cortisone on other physiologic functions.

PROCEDURE

The same regimen was used in both 1953 and 1954. The patients were hospitalized during the study, and their customary program of a regular diet without supplemental potassium was continued. Daily maintenance doses of cortisone were continued unchanged. Patients entered the hospital in the late afternoon, and the following morning the collection of control urine specimens was begun. The first 24-hour period, which served as the control period, was designated as Day 0 (See Fig. 1). The next five days were test days, which were designated Day 1 through 5, consecutively. The urine collected was kept refrigerated without preservative and assayed for 17-ketosteroids and 17,21-dihydroxy-20-ketosteroids. Twenty-four-hour creatinine excretions were also determined to provide some check on the accuracy of collection. On Day 1, 25 units of corticotropin † in 500 cc. of 5% dextrose in water was given intravenously over a three-hour period, starting at 9:00 a. m. The same dosage was repeated on Day 2. On Days 3, 4, and 5, corticotropin, 25 units in 1000 cc. of 5% dextrose in water, was given intravenously over a 16-hour period, starting at 9:00 a. m. Thus, on the tables to follow, the day number represents the number of infusions of corticotropin which were completed at the time of closing that day's urine collection.

Circulating eosinophiles were counted in the morning of Days 1 through 5 at approximately 8:00 a. m. under fasting conditions and again at 3:00 p. m., which was six hours after the start of the intravenous infusions.

At 1:30 p. m. on Day 0, each patient was given a radioactive iodine tracer dose, and 24 hours later, on Day 1, the activity over the gland was measured. During this 24-hour period, the patient completed the first 3-hour intravenous infusion of corticotropin, and so the results of the uptake studies do not represent strict precorticotropin values. However, since the infusion was started only four hours before the iodine uptake was measured, a significant effect on the thyroid seems unlikely.

Determinations of basal metabolic rate, serum cholesterol-cholesterol ester ratio, serum protein-bound iodine, fasting blood sugar, and serum electrolytes were completed the morning of Day 1,

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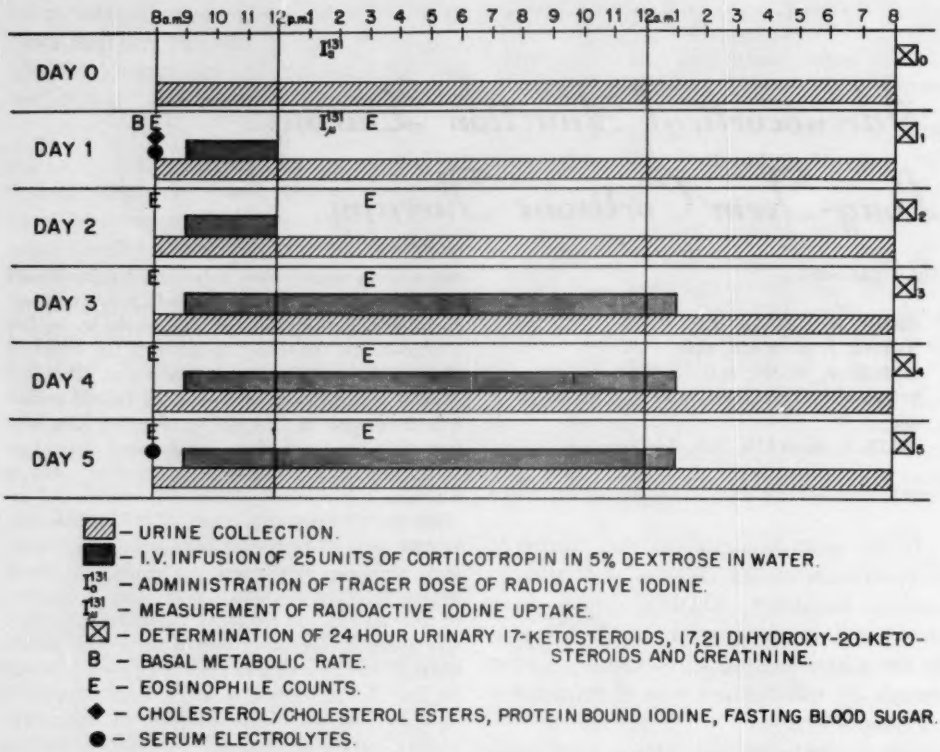
* References 2, 5, 14, and 15.

† ACTHAR, Armour brand of adrenocorticotropic hormone, lyophilized, equivalent to 25 mg. standard LA-1-A.



▨ — URINE COLLECTION.
■ — I.V. INFUSION OF 25 UNITS OF CORTICOTROPIN IN 5% DEXTROSE IN WATER.
I_o^{131} — ADMINISTRATION OF TRACER DOSE OF RADIOACTIVE IODINE.
I_{24}^{131} — MEASUREMENT OF RADIOACTIVE IODINE UPTAKE.
⊠ — DETERMINATION OF 24 HOUR URINARY 17-KETOSTEROIDS, 17,21 DIHYDROXY-20-KETOSTEROIDS AND CREATININE.
B — BASAL METABOLIC RATE.
E — EOSINOPHILE COUNTS.
◆ — CHOLESTEROL/CHOLESTEROL ESTERS, PROTEIN BOUND IODINE, FASTING BLOOD SUGAR.
● — SERUM ELECTROLYTES.

Fig. 1.—Program of study of patients receiving long-term therapy with cortisone.

prior to beginning the initial infusion of corticotropin. Serum electrolyte determinations were repeated on Day 5, after four consecutive days of adrenocortical stimulation with corticotropin.

In spite of all precautions, some 24-hour urine collections were inaccurate and infusions did not terminate exactly at the time planned. Physical activity and other factors were not constant. These variations render the data only roughly quantitative.

METHODS

Eosinophiles were counted by Pilot's [9] method. Urinary 17-ketosteriods were determined according to the method outlined by Drekter and co-workers,[1] and urinary corticoids (17, 21-dihydroxy-20-ketosteroids) were determined according to the method outlined by Porter and Silber.[10] Cholesterol-cholesterol esters were measured by a modified Schoenheimer-Sperry[13] technique. Fasting blood sugar was measured by a modified Folin-Wu method, with zinc hydroxide precipitation of protein. Serum sodium and potassium levels were measured on the Beckman DU flame photometer. Chloride was measured according to the method of Schales and Schales.[12] Serum CO_2 content was determined by gasometric analysis with the Van Slyke apparatus.

CRITERIA FOR EVALUATION OF ADRENOCORTICAL RESPONSIVENESS

In evaluating adrenocortical responsiveness, the values obtained after the daily intravenous infusions of corticotropin were compared with those obtained during the control period. Adrenocortical response was considered adequate if two of the following three criteria were met:

(1) Eosinophiles: a decrease of more than 60% in circulating eosinophiles compared to the fasting count on Day 1

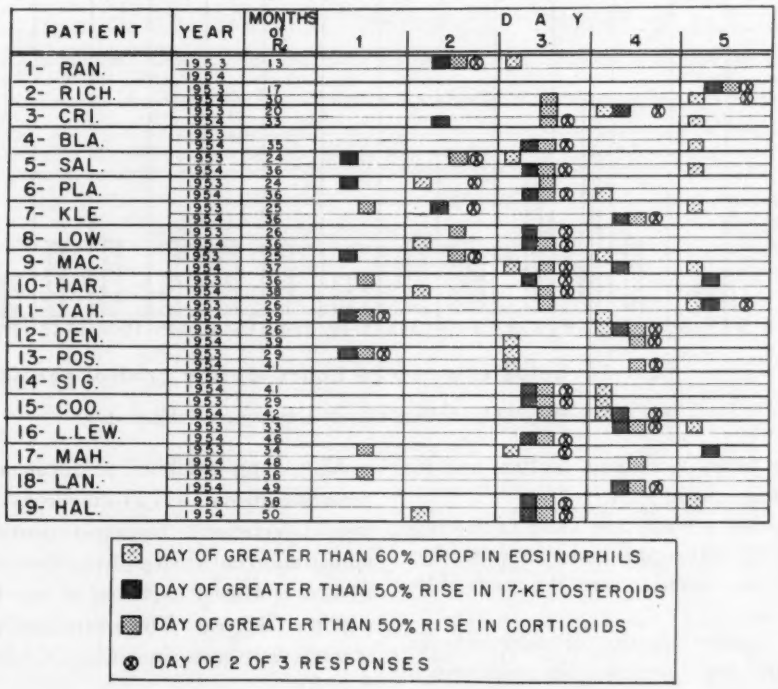
(2) 17-Ketosteroids: an increase of more than 50% in the 24-hour excretion compared to the control of Day 0

(3) Corticoids (17,21-dihydroxy-20-ketosteroids): an increase of more than 50%, with a minimum rise of 0.5 mg., in the 24-hour excretion compared to the control of Day 0. The normal values with the method employed [10] range from 0 to 1.0 mg. per 24 hours. A rise of 0.5 mg. is considered significant.

TABLE 1.—*Entry Data on Patients Receiving Long-Term Treatment with Cortisone*

Patient	Diagnosis	Cortisone, Mg./Day	Age in 1954, Yr.	Months of Continuous Treatment		Uncorrected Wintrobe Sed. Rate		Hemoglobin, Gm.		Fasting Blood Sugar	
				1953	1954	1953	1954	1953	1954	1953	1954
1. Ran	Rh. arthritis	50-75	33	13	..	9	..	16.4	....	71	..
2. Rich	Rh. arthritis	75-100	59	17	30	47	11	12	13.1	60	60
3. Cri	Scleroderma	75-100	33	20	33	16	4	17.9	16.8	60	47
4. Bla	Rh. arthritis	50-75	..	..	35	..	35	....	15.5	..	71
5. Sal	Rh. arthritis	75-100	38	24	36	35	25	14.6	14.6	63	63
6. Pla	Boeck's sarcoid	25-150	56	24	36	27	17	15.9	17.3	63	74
7. Kle	Asthma	75-100	55	25	36	4	1	15.9	15.1	71	66
8. Low	Rh. arthritis	50-75	37	26	36	42	28	14.1	....	52	113
9. Mac	Rh. arthritis	50-75	28	25	37	13	36	14.2	13.3	66	40
10. Har	Rh. arthritis	75-100	44	26	38	28	32	15.5	15.9	52	60
11. Yah	Rh. arthritis	50-75	29	26	39	24	21	15.5	14.2	66	50
12. Denn	Rh. arthritis	50-75	35	26	39	17	7	15.5	15.9	60	47
13. Pos	Rh. arthritis	75-100	49	29	41	45	38	13.9	13.1	68	61
14. Sig	Dermatitis Diabetes mellitus	75-100	42	..	41	..	5	....	16.8	..	120
15. Coo	Rh. arthritis	50-75	32	29	42	25	20	15.5	15.5	58	68
16. L. Lew	Rh. arthritis	75-100	60	33	46	19	6	16.8	16.4	58	44
17. Mah	Rh. arthritis	50-75	41	34	48	13	25	14	14	63	66
18. Lan	Rh. arthritis	50-75	55	36	49	28	30	15.1	15.5	56	55
19. Hal	Rh. arthritis	50-75	65	38	50	29	22	15.1	13.1	63	50

TABLE 2.—*Results of Adrenocortical Stimulation with Corticotropin*



The day of satisfactory decrease in eosinophiles was selected as follows:

(a) The first day on which both daily eosinophile counts showed a greater than 60% decrease or

(*b*) The second day on which one of the two daily eosinophile counts showed a greater than 60% decrease.

The day on which satisfactory rise in 17-ketosteroids and urinary corticoids occurred was selected as follows:

(*a*) The first day on which a greater than 50% rise occurred (with a minimum rise of 0.5 mg. of corticoids) was selected, provided a similar or greater rise was obtained on the following day, or

(*b*) If the required rise was not obtained on successive days then the second day on which such a rise occurred was selected as the day of response.

RESULTS

The study included 19 male patients, who had received continuous therapy with cortisone for 13 to 38 months in 1953 and for 30 to 50 months in 1954.

Entry data are given in Table 1. A range of dosage of cortisone is given for each, since the dose was varied to meet the needs of the patient.

The detailed results of adrenocortical stimulation with corticotropin are shown in Table 2.

Three patients (Patients 2, 8, and 18) in the year 1953 and four patients (Patients 7, 16, 17, and 18) in the year 1954 failed to show a greater than 60% decrease in eosinophiles.

In 1953, one patient (Patient 18) did not have a greater than 50% rise in 17-ketosteroid excretion; however, the urine collection for Day 4 was incomplete. In 1954, four patients (Patients 2, 12, 13, and 17) failed to show an adequate rise in 17-ketosteroid excretion. However, the control excretion for these four patients ranged from 13.7 to 16.7 mg. per 24 hours. A marked difference in the range of control excretions is shown for the years 1953 and 1954 (See Fig. 2).

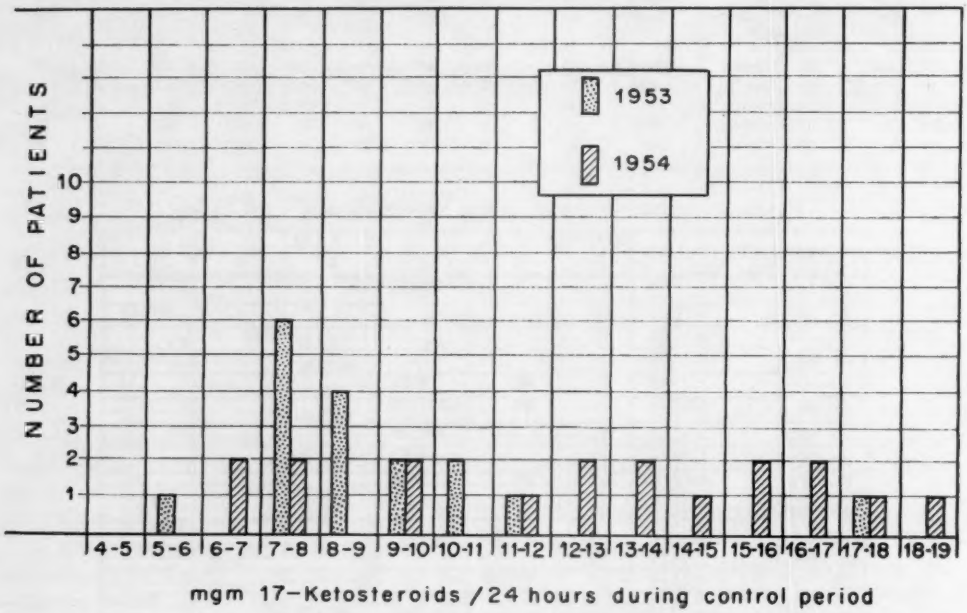


Fig. 2.—Urinary 17-ketosteroid excretion during control period.

All patients exhibited an adequate rise in urinary corticoids (17,21-dihydroxy-20-ketosteroid excretion). During corticotropin administration only two patients showed a peak 24-hour corticoid excretion of less than 1.0 mg. in either year. The control and peak excretions were quite similar in both years (See Fig. 3).

Two of the patients had fasting "true" blood sugar concentration greater than 110 mg. per 100 cc. in 1954. In one patient (Patient 14) the elevation of fasting blood sugar concentration appeared first after about a

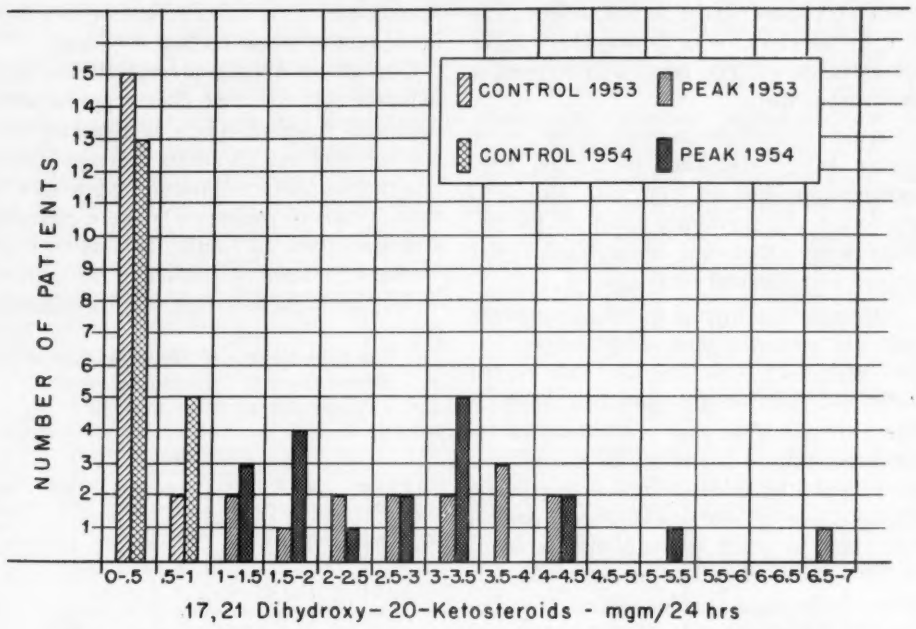


Fig. 3.—Urinary corticoid excretion during control period compared with peak excretion during test period.

TABLE 3.—*Data Regarding Thyroid Function in Patients Receiving Long-Term Cortisone Therapy*

Patient	Months of Therapy in 1954	Basal Metabolic Rate				PBI,* γ/100 Ml.				24 Hr. I^{131} Uptake, % of Administered Dose			
		1951	1952	1953	1954	1951	1952	1953	1954	1951	1952	1953	1954
1. Ran	..	....	....	+ 2	....	...	...	7.2	...	..	..	23	..
2. Rich	30	....	....	—11	—12	...	...	6.2	4.3	..	..	24	31
3. Cri	33	—11	....	+ 6	—15	5.6	...	7.4	6.4	23 33	..	38	42
4. Bla	35	....	....	+12	+17	7.1	...	8.0	5.7	19	..	19	28
5. Sal	36	+ 7	....	— 6	— 4	4.3	4.9	6.1	4.2	22	34	21	31
6. Pla	36	— 7	....	—14	—18	4.6	3.6	6.7	5.6	15 26	16	19	17
7. Kle	36	+20	....	....	+10	7.6	6.7	10.9	7.5	23	30	19	15
8. Low	36	— 5	....	—11	+ 8	4.5	6.0	6.5	6.4	40	36	20	29
9. Mac	37	....	—11	— 3	— 8	5.4	5.2	6.9	7.0	38	19	20	18
10. Har	38	....	....	— 4	— 3	...	4.5	6.8	6.0	..	12	15	16
11. Yah	39	....	....	+ 1	— 4	...	2.8	6.3	4.9	30	14	33	31
12. Denn	39	....	....	—11	— 8	6.3	5.7	7.2	5.7	20	18	22	24
13. Pos	41	....	....	— 2	— 3	5.4	4.6	6.6	7.0	16	5	8	12
14. Sig	41	—12	....	....	— 2	4.8	5.8	...	6.5	20	15	..	20
15. Coo	42	....	—14	— 3	—14	4.4	4.8	6.7	4.8	29	22	13	31
16. L. Lew	46	....	—12	— 2	+ 8	5.1	6.1	6.4	5.7	17 10	19	17	23
17. Mah	48	....	....	— 4	—16	4.7	4.3	6.1	5.0	18 13	24	20	29
18. Lan	49	....	....	+ 1	—21	4.2	4.2	6.9	5.2	..	27	24	27
19. Hal	50	....	....	+22	+12	...	6.1	7.4	4.7	..	28	33	26

* PBI, protein-bound iodine.

year on cortisone; in the second patient (Patient 8) the elevation of fasting blood sugar concentration was first noted after 36 months on cortisone therapy.

Serum electrolyte concentrations were studied before and after stimulation with corticotropin, and no significant alteration was found. As previously noted, all the patients were maintained on a regular diet without supplemental potassium.

Suppression of thyroid function in patients receiving cortisone and corticotropin has been reported.‡ Our findings with regard to thyroid function are shown in Table 3. There are numerous gaps in the data, but no consistent pattern is shown. In the individual patients the values of radioactive iodine uptake varied without any consistent pattern from year to year. Red cell-plasma ratios of I^{131} were not available in every case, but where determined were consistent with the iodine-uptake values.[18] Cholesterol-cholesterol ester ratios showed no typical alteration and were not included in Table 3. In the patients herein described, the maintenance doses of cortisone did not appear to alter significantly their thyroid function.

COMMENT

Similar studies of the adrenocortical response to stimulation with corticotropin were performed in 1951 on four of the patients and in 1952 [2] on 14 of the patients reported in the present work. A comparison of the number of days of stimulation with corticotropin required for adrenocortical response is shown in Table 4. A composite presentation of the results of 35 studies performed on 19 patients in 1953 and 1954 is shown in Table 5.

A study of these tables suggests that as treatment is prolonged there is slower response of adrenal cortex to stimulation with corticotropin. However, such a conclusion may not be warranted. The criteria for the selection of the day of adrenocortical response were established arbitrarily. The errors inherent in the methods used in the collection of the data presented could easily have caused a deviation of one or two days in the time of adrenocortical response.

Our previous [2] and present studies have indicated that cortisone does suppress adrenocortical function. There is abundant supporting evidence. Various workers § have reported on the morphologic appearance of the adrenals of patients who were receiving cortisone prior to death. Solassa and coworkers [11] found a reduction in adrenal weight in all patients receiving cortisone for more than 5 days if the course of therapy extended to within 20 days of the patient's death. If the drug had been discontinued more than 21 days prior to death, no significant weight change was observed. Microscopically, the adrenals of patients receiving cortisone showed a fairly characteristic group of changes.‖ There was atrophy of zona

TABLE 4.—*Number of Successive Days of Stimulation with Corticotropin Required for Adrenocortical Response*

Patient	1951 *	1952 A *	1952 B †	1952 C ‡	1953	1954
1. Ran	..	Not done	..	..	2	Not done
2. Rich	..	Not done	..	..	5	5
3. Cri	..	Not done	..	..	4	3
4. Bla	..	Not done	..	..	Not done	3
5. Sal	4	..	4	..	2	3
6. Pla	..	..	..	4	2	3
7. Kle	..	..	3	..	2	4
8. Low	4	..	4	..	3	3
9. Mac	4	2	..	..	2	3
10. Har	..	..	..	5	3	3
11. Yah	..	2	..	..	5	1
12. Denn	..	Not done	..	..	4	4
13. Pos	..	3	..	..	1	4
14. Sig	..	1	..	..	Not done	3
15. Coo	..	3	..	..	3	4
16. L. Lew	..	1	..	..	4	3
17. Mah	3	3	..	..	3	No response
18. Lan	..	..	..	3	No response	4
19. Hal	..	2	..	..	3	3

* Corticotropin, 25 mg. in 1,000 cc. 5% dextrose in water to run 16 hours intravenously daily.
† Identical regimen to that of the present study.
‡ Corticotropin, 25 mg. in 500 cc. 5% dextrose in water to run 3 hours intravenously daily for two successive days, followed by intramuscular injection of 40 mg. corticotropin gel every 12 hours.

‡ References 4, 16, and 17.

§ References 8 and 11.

‖ References 8 and 11.

fasciculata and zona reticularis, and an increasing degree of atrophy was noted in direct relationship to longer periods of therapy. The zona glomerulosa appeared broadened or more prominent, and the cells were of normal size. There was some decrease in sudanophilic material in all layers of the cortex, but this loss was most marked in the zona fasciculata. Although there was a reduced concentration of sudanophilic material in the zona glomerulosa, it was present as intracellular globules and fine granules. The zona reticularis appeared to lose its lipid last and patient the medication was discontinued 17 days before death. At necropsy there was evidence of reversal of the atrophy, with the cells of the outer fascicular layer reverting to normal size. Another patient had not received cortisone for 51 days prior to death, and in this case the zona glomerulosa was of normal width, the cells of the fascicular and reticular layers were hypertrophic, and there was marked reduction of lipids in all parts of the cortex. These changes were similar to those found in patients who had received corticotropin prior to death.

TABLE 5.—*Composite Results of Thirty-Five Studies on Nineteen Patients in 1953 and 1954*

MOS. of Rx	TOTAL PTS.	RESPONSE																					
		EOSINOPHIL						17-KETOSTEROID						E. CORTICOID						ADRENAL (2/3)					
		DAY					*	DAY					*	DAY					*	DAY					*
		1	2	3	4	5		1	2	3	4	5		1	2	3	4	5		1	2	3	4	5	
10-15	1			●				●							●							●			
16-20	2				●		●				●	●				●		●					●	●	
21-25	4		●	●	●	●		●●	●					●	●●	●					●●				
26-30	7			●	●●	●●●	●	●		●●	●	●	●	●●	●	●●	●			●		●●	●	●●	
31-35	4			●		●●			●	●	●	●		●		●	●					●●	●		
36-40	10		●●	●●	●●	●●	●●	●		●●	●●	●	●●	●●		●●●	●●			●		●●●	●●		●
41-45	3			●	●●					●	●		●			●●	●					●	●●		
46-50	4		●				●●			●●	●		●			●●	●●					●●	●		●

* No response obtained within five days

to a lesser degree. It has been pointed out ¶ that the adrenal changes found in patients treated with cortisone resemble those seen in patients who had clinical and necropsy evidence of hypopituitarism. Consequently, it has been postulated that exogenous cortisone induces adrenal atrophy by suppressing the secretion of pituitary adrenocorticotropic hormone.

Our studies indicate that this cortisone-induced adrenal atrophy is reversible. O'Donnell, Fajans, and Weinbaum [8] had two patients in their series in whom the microscopic findings likewise suggested that cortisone-induced atrophy is reversible. In one

While it is reassuring to have evidence of the reversibility of cortisone-induced atrophy of the adrenal cortex, another part of the picture must be kept constantly in mind. There have been several cases of postoperative irreversible shock and death of patients who had been on cortisone therapy prior to surgery.# In one such patient, oral cortisone had been discontinued five months prior to surgery and only six intra-articular injections of hydrocortisone, totaling 422 mg., had been given during the interval. This untoward event is presumably due to suppression of the pituitary and adrenal subsequent to therapy with cortisone. It follows that any

¶ References 8 and 14.

References 3, 7, and 11.

patient who is or has recently been receiving cortisone may require additional cortisone for maintenance through any period of stress.

SUMMARY

In this study of 19 patients, the adrenal cortex was suppressed by the continuous administration of cortisone but remained responsive to stimulation with corticotropin. It is uncertain whether the degree of suppression was increased as the period of therapy with cortisone was extended.

The inability of the suppressed adrenal cortex to respond quickly to corticotropin must be borne in mind constantly in managing patients who are receiving cortisone. In any illness or injury constituting a stress, the need for additional exogenous cortisone must be anticipated.

Long-term therapy with cortisone was not shown to produce any characteristic change of thyroid function or serum electrolytes.

Mr. Wilbert R. King, Miss Eleanor Enos, and Miss Barbara Chapman performed the chemical determinations on the 24-hour urine specimens. The radioactive-iodine-uptake studies were performed by the isotope unit, under the direction of Dr. William A. Reilly. The other laboratory procedures were performed in the clinical laboratory, under the direction of Dr. Thomas V. Feichtmeir. The art work was done by Miss Kay Hyde. The manuscripts were prepared by Mrs. Irene M. Gorman.

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Origin of Erythromycin-Resistant Strains of Micrococcus Pyogenes in Infections

Bacteriophage Types and In Vitro Resistance of Cultures to Antibiotics

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Since the introduction of erythromycin in 1952 by McGuire and co-workers [1] and the first reports of its clinical application,* there has been increasing use of this antibiotic in the treatment of infectious diseases. It has been particularly effective in the treatment of infections caused by staphylococci which are resistant to penicillin and to other antibiotics.† Few strains of staphylococci isolated from infections shortly after the introduction of this antibiotic were found to be resistant to erythromycin in concentrations too great for clinical use.‡ According to Haight and Finland,[9] in 1952 all of 640 strains of staphylococci were sensitive to erythromycin in concentrations of 1.56γ/ml.; 96% were inhibited by 0.2 to 0.8γ/ml., and 87% were sensitive to 0.4γ/ml.

Increased resistance to erythromycin occurs in vitro when strains of staphylococci are cultivated in increasing concentrations of erythromycin.§ Erythromycin-resistant strains of staphylococci have been found in the nasopharynges of hospital personnel after erythromycin was used in the treatment of patients.‖ Prior to the use of erythromycin in the treatment of patients, all strains of Staphylococcus isolated from the staff and employees were sensitive to erythromycin; however, a survey of the personnel five months after the use of erythromycin for patients disclosed that 75% of the strains were resistant to 100γ/ml. of erythromycin. Martin and co-workers [13] isolated erythromycin-resistant strains of Staphylococcus from 37 patients in the period from February, 1952, to February, 1954. It is evident from these reports that strains of Micrococcus pyogenes have emerged with increased resistance to erythromycin.

The purposes of this investigation were as follows: (1) to attempt the detection of erythromycin-resistant strains of staphylococci in infections, (2) to obtain information regarding the mode of origin of strains with increased resistance, (3) to study evidence of cross infections by erythromycin-resistant staphylococci in hospitalized patients, and (4) to determine the susceptibility of erythromycin-resistant strains to other antibiotics.

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METHODS OF STUDY

Erythromycin was first used in the treatment of infections at Minneapolis General Hospital in December, 1952. Strains of M. pyogenes var. aureus were isolated from sputum, blood, pus, empyema fluid, and drainage from infected wounds. All strains were tested for hemolysin and coagulase production. The in vitro susceptibility of all strains was determined for penicillin, streptomycin, chlortetracycline, oxytetracycline, chloramphenicol, bacitracin, carbomycin, neomycin, and erythromycin. The standard twofold tube-dilution technique was used for the sensitivity tests.[14] All cultures were typed with 34 strains of staphylococcal bacteriophages.[15]

RESULTS

Two hundred eight cultures of M. pyogenes were isolated from Dec. 1, 1952, to March 1, 1954, at the Minneapolis General Hospital, and sensitivity tests were performed on these strains. Cultures from one patient at the University of Minnesota Hospitals were included in this study. The first strain of erythromycin-resistant Staphylococcus was isolated from an infection at the Minneapolis General Hospital in June, 1953. A total of 37 cultures of erthromycin-resistant staphylococci were obtained from 23 patients during this period. All strains were hemolytic and produced coagulase. A summary of results of in vitro sensitivity studies with erythromycin for each year is shown in Table 1. Strains which were not inhibited by 3.1γ or less per milliliter were called resistant. No erythromycin-resistant staphylococci were obtained in 1952. In 1953, 20.9% were resistant to 3.1γ of erythromycin per milliliter. Most erythromycin-resistant strains in this study required from 200 to 400γ per milliliter for inhibition of growth.

TABLE 1.—*Concentrations of Erythromycin Required to Inhibit Growth of Staphylococci Isolated at the Minneapolis General Hospital*

Year	Total Cultures	Per Cent of Cultures Inhibited by Various Concentrations of Erythromycin, γ/Ml.			
		0.09-3.1	6.3-12.5	25-50	>50
1952.....	30	100.0	0	0	0
1953.....	153	79.1	1.3	1.3	18.3
Jan. 1-March 1, 1954.....	25	84.0	0	0	16.0

Summaries of the clinical and laboratory findings are presented in Tables 2 and 3. Seven of the 23 patients died. All strains were resistant to 3.1γ per milliliter of penicillin, streptomycin, chloramphenicol, erythromycin, and carbomycin. All but one culture were resistant to oxytetracycline and chlortetracycline. There was moderate resistance to bacitracin, and all the cultures were sensitive to neomycin. Twenty of 23 cultures were not inhibited by 25,000γ per milliliter of streptomycin, and 100 to 1600 units of penicillin per milliliter were required to inhibit 22 of the 23 cultures. All strains possessed similar degrees of resistance to erythromycin and carbomycin.

Of the 23 patients infected with erythromycin-resistant staphylococci, 11 had never received erythromycin and 1 had received the antibiotic 21 days prior to isolation of the resistant culture. Seven of the patients who had not received erythromycin had surgical wound infections. These results indicate that cross infections occurred in the hospital.

Bacteriophage typing of the staphylococci revealed that all strains (with exception of two cultures which were nontypable) were in Group III. It has been reported that the majority of penicillin-resistant staphylococci are of Type 6/47 of Group III.¶ In this study, the strains were lysed by Type 53 of Group III in 13 of the 23 patients (Table 2). Six of these 13 patients (Patients 3, 4, 7, 10, 12, and 17) had wound or skin infections. It is probable that Type 53 emerged as the predominant erythromycin-resistant strain in the environment of the hospital.

In discussing the results of bacteriophage typing of the cultures, the patients are divided into the following four groups:

Group 1: No change occurred in the bacteriophage type of Staphylococcus during

¶ Knight, V., and Holzer, A. R.: Phage Type and Antibiotic Susceptibility of Micrococcus Pyogenes Var. Aureus Strains from Hospital Patients, in Antibiotics Annual, [12] p. 328, and Roerig, R. N.; Metzger, J. F.; Fucillo, M. H., and Ernst, K. F.: Phage Typing of Antibiotic-Resistant Staphylococci: II. Phage Types of Organisms Isolated from Various Sources, in Antibiotics Annual,[12] p. 329.

TABLE 2.—*Summary of Clinical and Laboratory Data of Twenty-Three Cases of Staphylococcal Infections*

No.	Patient	Age	Sex	Admission	Date of 1st Resistant Culture	No. of Resistant Cultures	Diagnosis	Source of Resistant Strain	Erythromycin Therapy, Days	Bacteriophage Type		Antibiotics Used*	Result
										Erythromycin-Sensitive	Erythromycin-Resistant		
1	E. B.	56	M	12/13/52	5/18/53	8	Acute bacterial endocarditis	Blood	146	6/47/VA$_4$; 44A	VA$_4$; 6/31A; 53	CM, E, P, B, N	Died
2	F. P.	39	M	5/24/53	6/ 2/53	1	Cerebral artery thrombosis; septicemia	Blood	0	.....	53	P, OT	Recovered
3	E. B.	52	F	6/ 4/53	6/14/53	1	Pernicious anemia; cholecystitis	Wound	0	.....	53	P, SM, G	Recovered
4	J. R.	68	M	5/26/53	6/16/53	1	Chronic pulmonary disease; cholecystectomy	Wound	0	.....	53	P, SM, OT	Recovered
5	R. T.	33	M	6/11/53	7/ 6/53	1	Alcoholism; lobar pneumonia	Sputum	1 day 21 days prior to therapy	.....	53	P, SM, OT, N	Recovered
6	J. Z.	59	M	5/20/53	7/ 8/53	2	Agranulocytosis; pneumonia	Blood	8	47/53/75/77	53/77	OT, E, N	Died
7	F. T.	40	M	7/ 3/53	7/15/53	3	Fractures of tibia and fibula	Wound	0	.....	53	P, OT, SM	Improved
8	J. C.	53	M	8/21/53	9/14/53	1	Ruptured appendix; peritonitis	Sputum	9	.....	47/47C/53/75/77	P, SM, OT, E, CA	Died
9	W. W.	66	M	8/ 8/53	9/24/53	1	Perforated duodenum; peritonitis, septicemia	Blood	0	.....	VA$_4$/31/53/54	P, OT, SM	Died
10	H. H.	68	M	5/30/53	9/28/53	3	Alcoholism; diabetes mellitus; osteomyelitis	Wound	25	47/47C/54/75	53	P, OT, SM, E	Improved
11	T. D.	73	M	10/ 7/53	10/19/53	1	Arteriosclerosis obliterans; osteomyelitis	Ulcer	0	.....	47/VA$_4$/54/75	P, OT, SM, G	Improved
12	C. E.	62	F	9/12/53	10/26/53	1	Cerebral artery thrombosis; acute bacterial endocarditis	Pustule	12	VA$_4$	53	P, OT, SM, G, E	Improved
13	H. K.	42	F	10/20/53	10/31/53	2	Septicemia	Blood	7	7	7	CT, SD, OTB	Recovered
14	M. M.	28	F	10/ 5/53	10/31/53	1	Herniated nucleus pulposis, operated	Wound	0	.....	47/54/75	P, SM	Recovered
15	R. M.	72	F	9/15/53	11/10/53	1	Operative wound infection; fracture of femur; septicemia	Wound	39	VA$_4$	VA$_4$	P, SM, OT, G, N, E	Died
16	J. L.	46	M	11/ 1/53	11/13/53	3	Alcoholism; chest trauma; empyema	Pleural fluid	0	.....	53	P, SM	Improved
17	S. H.	75	M	11/ 8/53	11/23/53	1	Operative wound infection; herniorrhaphy	Wound	0	.....	47/53/54/75	P, SM	Recovered
18	E. B.	72	F	12/ 6/53	12/15/53	1	Operative wound infection; fracture of hip	Throat	5	.....	47	E, OT, G	Recovered
19	H. R.	69	M	11/30/53	12/23/53	1	Head injury; brain abscess	Brain abscess	0	.....	47	P, SM, OT, N, B, CA	Died
20	N. P.	70	M	11/ 9/53	1/13/54	1	Fracture humerus	Wound	47	.....	47/54	E, P, SM, G	Improved
21	J. F.	53	M	12/19/53	1/ 3/54	2	Bullet wound in head with brain abscess	Wound	10	.....	47	E, P, SM, OT, N, B	Improved
22	M. C.	48	F	1/ 7/53	2/19/53	1	Bartholin cyst	Cyst	0	.....	N. T.†	OT	Recovered
23	A. M.	68	M	2/ 5/54	2/22/54	1	Alcoholism; pneumonia	Stool	8	.....	N. T.	P, SM, OT, E	Died

* P, penicillin; SM, streptomycin; CT, chlortetracycline; OT, oxytetracycline; G, sulfisoxazole (Gantrisin); CA, chloramphenicol; E, erythromycin; CM, carbomycin; N, neomycin; B, bacitracin; SD, sulfadiazine.

† N. T., not typable.

therapy, but erythromycin-resistance developed. Table 4 shows the results of cultures for three patients from whom sensitive strains were isolated prior to treatment with erythromycin and the subsequent emergence of erythromycin-resistant strains after therapy with this antibiotic. The bacteriophage type of the Staphylococcus remained the same in each case. All three patients had bacteremia; however, the erythromycin-resistant strain was isolated from an infected wound of Patient 15. In these three patients it may be postulated that the erythromycin selected out the resistant cells contained in the invading population of staphylococci, resulting in survival of the resistant cells and suppression of the sensitive organisms.

Group 2: A change occurred in the bacteriophage type of Staphylococcus during therapy, and the cultures isolated after therapy were resistant to erythromycin. In three cases the erythromycin-resistant strains isolated after therapy were of different bacteriophage types than were the sensitive strains isolated prior to therapy. These data are shown in Table 5. The primary cultures were susceptible to 0.38γ per milliliter in every case. Cultures isolated after therapy,

TABLE 3.—*Number of Strains Sensitive to Various Concentrations of Antibiotics**

Antibiotic	Units or γ/Ml. of Broth				
	0.38-3.1	6.3-12.5	25-100	200-1,600	25,000
Penicillin	..	..	5	18	..
Streptomycin	..	..	1	2	20
Chlortetracycline	1	..	..	22	..
Oxytetracycline	1	..	2	20	..
Chloramphenicol	..	15	8	..	..
Erythromycin	..	1	1	21	..
Carbomycin	..	1	1	21	..
Bacitracin	11	12	..	..	..
Neomycin	23	..	..	..	..

* Twenty-three strains from 23 patients are used in this analysis. The final culture was selected in those patients who had multiple cultures.

TABLE 4.—*Studies of M. Pyogenes Isolated Before and After Therapy with Erythromycin**

Patient	Before Treatment			After Treatment		
	Source	Bacteriophage Type	Erythromycin Sensitivity, γ/Ml.	Source	Bacteriophage Type	Erythromycin Sensitivity, γ/Ml.
6	Blood	47/53/75/77	0.75	Blood	53/77	400.0
13	Blood	7	0.75	Blood	7	50.0
15	Blood	VA_4	0.38	Wound	VA_4	12.5

* Strains of M. pyogenes were isolated before and after therapy with erythromycin. They were of the same bacteriophage type in each case but developed increased erythromycin resistance.

TABLE 5.—*Studies of M. Pyogenes Isolated Before and After Therapy with Erythromycin**

Patient	Before Treatment			After Treatment		
	Source	Bacteriophage Type	Erythromycin Sensitivity, γ/Ml.	Source	Bacteriophage Type	Erythromycin Sensitivity, γ/Ml.
1	Blood	44A	0.38	Blood	VA_4	400
		$6/47/VA_4$	0.38		6/31A	200
					53	200
10	Wound	47/47C/54/75	0.38	Wound	53	400
12	Blood	VA_4	0.38	Skin infection	53	400

* Strains of M. pyogenes were isolated before and after therapy with erythromycin. They were of different bacteriophage types in each case and possessed different degrees of resistance to erythromycin.

TABLE 6.—*Studies of M. Pyogenes Isolated During Therapy with Erythromycin*

Patient	Source of Culture	Bacteriophage Type	Erythromycin Sensitivity, γ/Ml.
5.....	Sputum	53	400
8.....	Sputum	47/47C/53/75/77	50
18.....	Throat	47	400
20.....	Wound	47/54	200
21.....	Wound	47	200
23.....	Stool	Nontypable	200

which were of different bacteriophage types in every case, required 200 to 400γ of erythromycin per milliliter for inhibition of growth. Patient 1 had staphylococcal endocarditis with chronic exfoliative dermatitis and recurrent infections of the skin. He was hospitalized for 17 months prior to his death. Different types of staphylococci were isolated from cultures of his blood during the long period in the hospital. The cultures from the other two patients were obtained from infected wounds, blood, and a skin infection. In Patient 12, who had staphylococcal bacteremia and developed an infection of the skin during therapy, the erythromycin-resistant strain from the secondary infection was of exogenous origin and did not represent a metastatic abscess. In all three cases, the staphylococci which were highly resistant to erythromycin were of Type 53. This strain was present in the environment of the hospital. It is evident that the three patients were infected with erythromycin-sensitive strains that perished during therapy and that the original causative organisms were replaced by resistant strains as a result of cross infection.

Group 3: No cultures were isolated prior to therapy; erythromycin-resistant strains were isolated during or after therapy with erythromycin. In six patients erythromycin was used in therapy, and staphylococci, which were highly resistant to erythromycin, were isolated after treatment was begun. These results are presented in Table 6. Since no cultures were obtained prior to therapy, it was impossible to compare bacteriophage types in individual patients. The highly resistant strains were lysed predominantly by bacteriophage Types 53 and 47. One culture was nontypable. Patient 23 developed severe diarrhea following treatment with penicillin, streptomycin, and oxytetracycline and was shown to have pseudomembranous enterocolitis. Stool cultures at the time of onset of diarrhea did not reveal large numbers of staphylococci. On the eighth day of therapy with erythromycin he died, and erythromycin-resistant staphylococci were isolated from the stool.

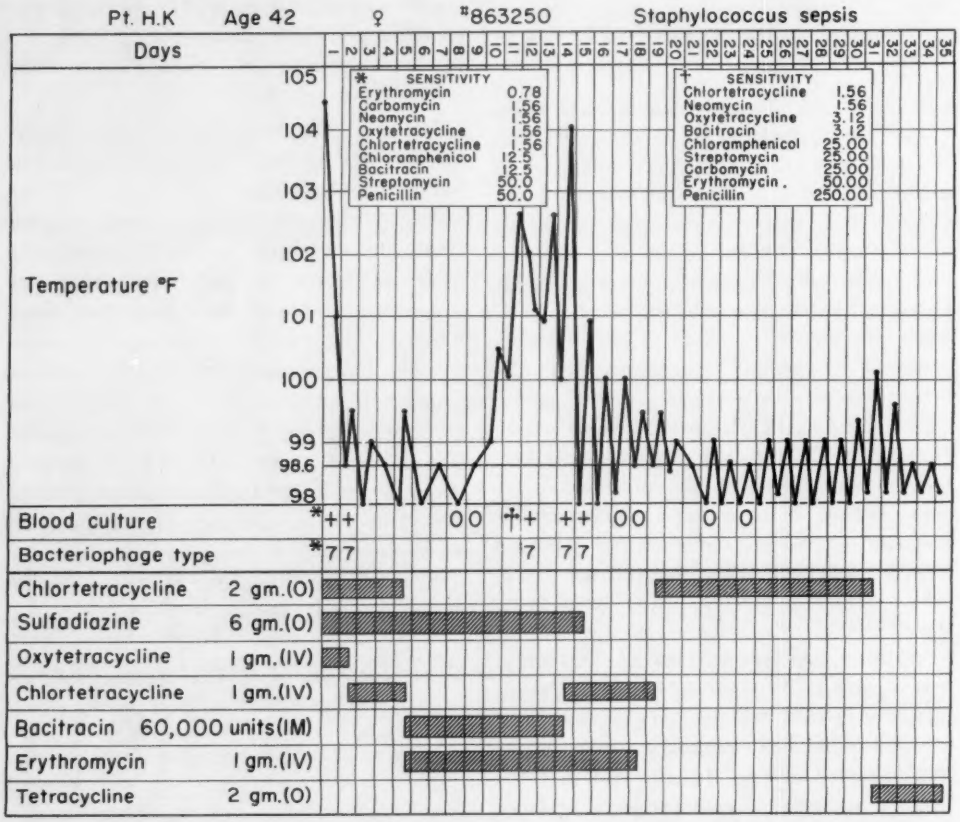
Group 4: Erythromycin-resistant staphylococci were isolated from infections in patients who were treated with antibiotics other than erythromycin. Eleven patients did not receive erythromycin but were treated with other antibiotics. In most cases, treatment consisted of combinations of penicillin, streptomycin, and one of the tetracycline compounds. The results of studies of the cultures isolated from this group of patients are presented in Table 7. The cultures required concentrations of 100γ to 400γ of erythromycin per milliliter for inhibition of growth. Seven of the 11 cultures of staphylococci were susceptible to bacteriophage Type 53. This is additional evidence of cross infection in hospitalized patients.

TABLE 7.—*Studies of M. Pyogenes Isolated from Patients Who Were Not Treated with Erythromycin*

Patient	Source of Culture	Bacteriophage Type	Erythromycin Sensitivity, γ/Ml.
2.....	Blood	53	400
3.....	Wound	53	400
4.....	Wound	53	400
7.....	Wound	53	400
9.....	Blood	VA_4/31/53/54	400
11.....	Leg ulcer	47/VA_4/54/75	100
14.....	Wound	47/54/75	400
16.....	Pleural fluid	53	400
17.....	Wound	47/53/54/75	400
19.....	Wound	47	400
22.....	Infected Bartholin cyst	Nontypable	400

The value of tests for antibiotic resistance in the management of infections and the aid provided by bacteriophage typing in investigations of staphylococcal sepsis are demonstrated by the following case report:

Patient 13, a 42-year-old woman, became ill on October 4, 1953, with chills, fever, headache, nausea, and vomiting. She was treated with penicillin and oxytetracycline, with improvement. On October 17, 1953, she developed weakness in the right leg, fever, and stiff neck. She was admitted to the University of Minnesota Hospitals on Oct. 18, 1953. Her subsequent course is shown in the Figure. Her temperature was 104.5 F. Physical examination revealed moderate nuchal rigidity and a soft apical systolic murmur. Laboratory studies showed 10,750 leucocytes per cubic millimeter of blood, with 82% neutrophiles, 17% lymphocytes, and 1% monocytes. The cerebrospinal fluid contained 2236 leucocytes per cubic millimeter, with 86% neutrophiles and 14% monocytes; 30 mg. protein and 55 mg. sugar per 100 cc. The urine was normal. Cultures of the cerebrospinal fluid and blood were obtained, and treatment with chlortetracycline, oxytetracycline, and sulfadiazine was begun. Culture of spinal fluid was sterile, and two blood cultures revealed M. pyogenes. Tests for antibiotic resistance revealed the causative organism to be sensitive to erythromycin in a concentration of 0.78γ per milliliter and to the tetracyclines in concentrations of 1.56γ per milliliter. The fever decreased rapidly with chlortetracycline and sulfadiazine, but therapy was changed on the fourth day to a combination of erythromycin, bacitracin, and sulfadiazine. Blood cultures remained sterile on the eighth and ninth days. On the 11th day the patient became febrile and blood cultures obtained on the 12th, 13th, and 14th days revealed M. pyogenes. Antibiotic sensitivity tests of the culture obtained on the 12th hospital day are presented in the Figure and show that the new culture required 50.0γ of erythromycin per milliliter for inhibition. Because of the increased resistance to erythromycin, the treatment was changed to chlortetracycline intravenously for five days with subsequent oral administration. The patient recovered. All of the five cultures of M. pyogenes recovered from this patient were lysed by



bacteriophage Type 7. Thus the same strain was present throughout her illness, but an increase in resistance to erythromycin of approximately 64-fold occurred during five days of therapy with erythromycin.

COMMENT

In this study, three patients had infections caused by staphylococci which became more resistant to erythromycin during treatment with the antibiotic. These cultures were of the same bacteriophage type before and after the emergence of resistant strains. The mechanism of the selective process is not clear; however, it can be concluded that there was a selection of bacterial cells with characteristics which enabled them to survive the treatment of erythromycin. The basic principles related to the appearance of antibiotic-resistant staphylococci have been reviewed by Spink.[16]

In three patients erythromycin-resistant staphylococci were isolated from infections following therapy with erythromycin, but the antibiotic-resistant strains were of a different bacteriophage type than the original causative agent. Either the infectious process contained a mixture of different types of Staphylococcus and the resistant strains survived or the original erythromycin-sensitive strains perished and were replaced by erythromycin-resistant strains during the period of therapy.

The staphylococci isolated from infections of six patients during therapy with erythromycin cannot be accurately identified with any source, since bacteriological studies on the patients prior to therapy were not carried out. These processes may be categorized as superinfections, as described by Weinstein and co-workers,[17] since they developed during therapy with antibiotics. Whether the strains were sensitive or resistant prior to therapy cannot be known. The fact that they were lysed predominantly by bacteriophage Types 53 and 47, which were most often found in the study as results of cross infections, would indicate that they were also spread by cross infection.

Cultures of erythromycin-resistant strains were isolated from 11 patients who did not receive erythromycin. In this group of cases there is no reason to suspect a selective process, and it can be concluded that cross infections occurred with erythromycin-resistant strains which were present in the environment of the hospital.

SUMMARY AND CONCLUSIONS

Twenty-three patients were observed from Dec. 1, 1952, to March 1, 1954, who developed infections caused by erythromycin-resistant staphylococci.

In three patients there was an increase in erythromycin resistance of staphylococci during treatment with erythromycin, without a change in bacteriophage type.

In three patients, the erythromycin-resistant strain isolated after therapy was a different bacteriophage type from the original erythromycin-sensitive Staphylococcus.

In six patients, who were receiving erythromycin, there was development of infections caused by erythromycin-resistant staphylococci.

Eleven patients, who did not receive erythromycin, developed infections which were caused by erythromycin-resistant staphylococci.

Infections with erythromycin-resistant staphylococci occur as a result of (*a*) the emergence of resistant staphylococci from the original sensitive strain by a process of selection and (*b*) cross infection by strains which are already resistant to the antibiotic.

Erythromycin-resistant strains isolated from infections possess a similar resistance to carbomycin.

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Staphylococcal Endocarditis

Some Clinical and Therapeutic Observations on Thirty-Eight Cases

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Infections due to Micrococcus pyogenes (Staphylococcus) are becoming increasingly difficult to manage because of the remarkable tendency of members of this genus to develop resistance to penicillin and other antibiotics. Although the individual strains vary considerably in this respect, the majority of staphylococci isolated from hospital patients and personnel in several clinics are currently being found to be penicillin-resistant.*

During the past few years we have followed the course of several patients with staphylococcal endocarditis. Of interest is a comparison of the results of therapy in this group with a much larger series obtained by reviewing the records of all such cases at the Johns Hopkins Hospital for the past 20 years. This series was divided arbitrarily into three periods. The first was 1933-1943, a time in which no well-established antibiotic treatment was available, although penicillin was used in a few of the later cases in doses which we now realize were inadequate. The second period, extending from 1944 through 1948, was expected to represent the time during which effective doses of penicillin were used with most strains of staphylococci still sensitive to that agent.† The third period includes the five years from 1949 through 1953. Of 12 cases in this group, 42% of the organisms were penicillin-resistant. One purpose of this study is to evaluate the special problems related to that complication.

During the 20-year period 1933 through 1953, there were 104 instances of staphylococcal bacteremia, excluding cases in which the bacteremia represented a terminal episode in patients who were near death from some unrelated disease. The present report is concerned with an analysis of the 38 patients in this group who we felt fulfilled the criteria for the diagnosis of staphylococcal endocarditis. Here the question of definition becomes somewhat difficult, and so we have established two categories. The first category includes 25 cases of endocarditis proved by autopsy, and the second includes 13 cases in which the diagnosis was "clinically certain." In the prepenicillin era nearly all patients with staphylococcal endocarditis died, but since then the infection has been cured often enough to bring up the question of whether or not the diagnosis is justified in patients who survive. The cases which qualified as clinically certain instances of acute endocarditis were those with repeatedly positive blood cultures in the presence of definite signs of some type of valvular disease, which may or may not have been present with the onset of the infection. Significant changes in the character of the murmurs while under observation or embolic phenomena of more than transient nature involving the skin, brain, lungs, kidneys, or other peripheral arteries were taken as further evidence in favor of endocarditis.

Of these 38 cases, 22 fell into the 10 years of Period I, 3 in the 5 years of Period II, and 13 in the 5 years of Period III. The striking fall in incidence in the second period

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* References 1-4.

† Only three cases of staphylococcal endocarditis were encountered in this middle period. One strain was sensitive to penicillin, being killed by 0.02 μ/cc.; the others were not tested.

TABLE 1.—*First Period*

	Name	Date	Age, Yr.	Underlying Disease*	Probable Focus	Valves	Chief Complications	Therapy	Results and Remarks
1.	P. J. 50893	1933	28	R. H. D.	Uterus	M	Meningitis	Bacteriophage	Died in 2 days
2.	H. R. 59055	1934	25	Cushing's disease, diabetes	Bladder	M	Pyelitis	.....	Died in 5 days
3.	L. F. 60657	1935	21	.....	Tubes	M	Meningitis	.....	Died in 3 days
4.	A. P. 67829	1936	57	Syphilitic aortitis	Abscess	A	Meningitis	Transfusions, antitoxin	Died in 2 days
5.	L. D. 74338	1936	19	R. H. D.	Dental infection	M	Acute glomerulo-nephritis, pericarditis	Antiserum, sulfanilamide (Prontylin)	Died in 2 mo. in uremia
6.	R. O. 113211	1937	51	B. P. H.	G. U. tract	A	Infected fistula (postop.)	Transfusions, antitoxin	Died in 12 days
7.	J. M. 122315	1937	17	R. H. D.	Mastoid	M A	Meningitis, cerebral embolus	Transfusions, lumbar punctures, sulfanilamide 5.4 gm. × 5 days	Died in 8 days; no operation performed
8.	A. H. 117154	1937	66	B. P. H.	G. U. tract	T	Pneumonia, prostatic infection	Transfusions	Died in 10 days
9.	D. H. 140926	1938	28	Congenital H. D.	.....	T M Septum	Heart failure	Sulfanilamide 6 gm. × 5½ wk.	Died in 7 wk., course presumably prolonged by therapy
10.	J. J. 157918	1938	83	B. P. H.	G. U. tract	Left ventricle	Pneumonia, myocardial infarct, pulmonary emboli	Sulfapyridine 3-12 gm. × 4 days	Died in 7 days; terminal septicemia in old man
11.	V. K. 115663	1938	23	Congenital H. D.	Pelvis	Ductus	Pulmonary infarct	Transfusions, antiserum, sulfanilamide 7 gm. × 4 wk.	Survived; prolonged subacute type (culture positive again 1939, not readmitted)
12.	H. M. 127928	1938	72	B. P. H.	G. U. tract	T M	Pyelitis	Transfusion, antiserum	Died in 11 days
13.	V. R. 188780	1939	43	Hypertension	.....	A M	Adrenal hemorrhages	Sulfanilamide, sulfapyridine	Died 4 hr. after admission, overwhelming septicemia
14.	M. B. 132691	1939	32	Infected abortion	Pelvis	M	Thrombosis of uterine veins	Sulfanilamide, sulfapyridine, antitoxin	Died 1 day after admission, overwhelming septicemia
15.	C. B. 193169	1940	76	Multiple myeloma	.....	T Left ventricle	Amyloid disease, pyelonephritis	Sulfathiazole	Died 2 days after admission
16.	E. B. 193250	1940	16	Congenital H. D.	.....	T P A	Meningitis, pericarditis	Sulfanilamide (1 dose)	Died 4 hours after admission
17.	L. B. 199941	1940	20	Congenital H. D., aortic insufficiency	.....	A	Heart failure	Sulfanilamide 6 gm. × 4 days, sulfapyridine 6 gm. × 7 days, sulfathiazole	Died; infection improved but died with fever and heart failure
18.	A. G. 207509	1940	26	Infected abortion	Pelvis	T	Pulmonary infarcts, serum hepatitis	Transfusions, staphylococcal toxin, sulfathiazole 6 gm./day	Died in 56 days, recurrent and persistent septicemia
19.	R. B. 222939	1941	56	Burns (infected), alcoholism	Skin	M	Meningitis, pericarditis, mycotic aneurysm	Transfusions, sulfadiazine spray for 4 days, 9 gm. × 2 days	Died in 12 days, alcoholic with severe burns
20.	I. J. 253175	1942	45	Carcinoma of bladder	Urinary tract	M	Bronchopneumonia	Nephrectomy, sulfonamide	Died in 10 days
21.	J. T. 299452	1943	36	.....	Skin	T	Lung abscesses	Sulfonamide, penicillin 240,000 units × 6 days (sensitive to 0.125 unit)	Died in 23 days, penicillin dose too small
22.	G. W. 306704	1943	67	A. S. H. D.	Skin	T M	Mycotic aneurysm, azotemia	Penicillin 220,000 units × 9 days (sensitivity unknown)	Died in 9 days, cultures became sterile but penicillin dose too small

* R. H. D., rheumatic heart disease; B. P. H., benign prostatic hypertrophy; A. S. H. D., arteriosclerotic heart disease.

parallels a similar fall in the occurrence of all the cases of staphylococcal bacteremia in our series during that time. This may be because penicillin was then available in adequate amounts for the therapy of all types of staphylococcal infections and a high percentage of strains were still sensitive. As a consequence, these infections were more readily controlled as they developed and so much less likely to result in invasion of the blood stream.

The group of patients in the last period of five years has been our main interest, with their special problems in diagnosis and therapy. It is encouraging to note that, by carrying out prolonged treatment with massive doses of penicillin and by continuing this with other antibiotics, the infection has been controlled in 7 of the 13 patients in the most recent group.

Some of the more pertinent problems are illustrated in the case reports and tables which follow.

TABLE 2.—*Second Period*

	Name	Date	Age	Underlying Disease	Probable Focus	Valves	Chief Complications	Therapy	Results and Remarks
23.	A. S. 285022	1944	82	Adenomata of prostate	G. U. tract	M	Myocardial and renal abscesses, hydrothorax	Sulfamerazine 2 gm. × 2 days, sulfathiazole 2 gm. × 7 days	Died in 11 days
24.	E. H. 452300	1948	19	R. H. D.	.....	M	Left ventricular aneurysm (? secondary to staphylococcal myocarditis)	Penicillin 10,000,000 × 2 days, 2,000,000 × 6 days, 4,000,000 × 7 wk. (penicillin sensitivity 0.02 units; streptomycin sensitivity 3.9 γ)	Survived; infection cured; strain very sensitive to penicillin
25.	G. S. 455815	1948	67	Diabetes, A. S. H. D.	Foot infection	A	Acute glomerulonephritis, renal failure	Penicillin 400,000-800,000 units × 7 days (sensitivity not done)	Died in 14 days; doses relatively small; cultures became sterile, but staphylococci found in infarcts at autopsy

REPORT OF CASES

CASE 1 (J. H. H. 138946‡).—C. L., a 61-year-old white man with known aortic regurgitation, thought to be secondary to syphilis, was admitted in 1944 for dilatation of the vesical neck. Immediately after this procedure the patient's temperature rose to 102.6 F and he developed polyarthritis. A blood culture taken at this time was reported as showing a heavy growth of M. pyogenes var. aureus. The patient received 160,000 units of penicillin a day for four days, and a sterile blood culture was obtained on the fourth day of treatment. During the seven-day period, during which three positive blood cultures were obtained, the patient's temperature ranged between normal and 103 F and the white cell count reached 21,000. Following cessation of penicillin therapy the patient remained afebrile, for one week, but died of renal failure.

At autopsy the mitral and aortic valves showed chronic endocarditis, presumably rheumatic, but no bacterial vegetations were seen. There were purulent prostatitis and multiple renal abscesses.

Comment.—This patient with rheumatic valvular heart disease had staphylococcal bacteremia for six days, with high fever, polyarthritis, and leucocytosis, but there were no bacterial vegetations on the heart valves at autopsy, 14 days after the onset of the infection.

CASE 2 (J. H. H. 650413).—G. H., a 17-year-old Negro youth, had a past history of two attacks of acute rheumatic fever resulting in mitral and aortic valvular disease. Twelve days prior to admission, in November, 1953, he developed a sore throat, fever, anorexia, and malaise. Prior to admission the patient had received a week's therapy with oral penicillin and sulfonamides, with some improvement in symptoms.

On admission he appeared only slightly ill. Temperature was 100.8 F; pulse, 88; blood pressure, 140/20. The classic signs of aortic insufficiency and mitral insufficiency were present. Neither petechiae nor splenomegaly was noted. Urinalysis revealed no red blood cells. The hematocrit value was 40%, and the white blood cell count was 8700. Six blood cultures were positive for a M. pyogenes var. aureus which was penicillin-resistant, being killed in vitro by a concentration of 50 units per cc., but was

‡ This case was not included in our series.

TABLE 3.—*Third Period*

Name, Date, and Age	Underlying Disease	Probable Focus	Valves	Chief Complication	Antibiotic Sensitivities*	Therapy†	Results and Remarks
A. Data on Six Patients Who Died							
26. K. E. 520004 1949 59	B. P. H.	G. U. tract	M	Cerebral hemorrhage, glomerulonephritis	Not done	Sulfadiazine, P, S, and A, (before admission)	Died 17 hr. after admission
27. R. M. 404684 1949 10	Congenital H. D. (tetralogy)	Anastomosis	Endarteritis (suture line)	Infarcts of brain and lung, postoperative aneurysm	P: 250 A: 0.09 S: 3.9 Ch: 6.2	P: 0.4 × 7 days 12-24 × 11 days 3 × 21 days S: 2 × 14 days A: 2-4 × 28 days Ch: 4 × 28 days	Died in 2½ months. Infection controlled with difficulty, then recurred; death due to pulmonary embolism
28. G. S. 433471 1951 30	Congenital H. D.	Dental extraction	Ductus	Glomerulonephritis, septic emboli, mycotic aneurysm	P: 1.9 Ch: 3.1 T: 0.19 A: 0.09	A. (in another hosp.) Ch: 6 × 3 days	Died 2 mo. after onset; 5 days after adm. terra. and pen. would have been preferable
29. V. C. 569777 1951 23	Ulcerative colitis	Colon	M	Meningitis, thrombophlebitis, pulmonary embolus	P: 0.25 A: S:	P: 3 per day A: S: Sulfisoxazole	Died in 35 days, severe septicemia in patient treated with corticotropin
30. L. M. 106268 1952 30	R. H. D.	Furuncle	M	Heart failure	P: 0.75 A: 0.05 T: 0.19 P: Res (disc)	P: 18 × 25 days A: 2 × 9 days E: 2 × 12 days	Died in 29 days; cultures sterile, but died with continuing infection and heart failure
31. M. S. 662115 1953 56	Congenital H. D.	Dental extraction	Septum T	Lung abscesses, duodenal ulcer	P: 0.8 A: 2+ (disc) T: 2+ (disc) E: 2+ (disc)	P: 16 × 25 days E: 3 × 12 days 2 × 11 days	Died 28 days after admission; blood cultures sterile last 18 days; complicated by cortisone therapy
B. Data on Seven Patients Who Survived							
32. R. C. 580441 1951 27	R. H. D. (treated S. B. E. in past)	Mastoid	M	Heart failure	P: 0.05 A: 3.1 Ch: 6.2 T: Res (disc)	P: 6-12 × 42 days 20 × 4 days A: 2 × 28 days (probenecid)	Survived; good response but patient in failure
33. J. S. 560346 1951 25	Pneumonia	Lungs	A	Emboli to popliteal and brachial arteries	P: 0.03 A: 0.05 Ch: 3.1	P: 0.6-3 × 5 days 6 × 51 days A: 4 × 8 days T: 4 × 4 days	Survived, cultures sterile after first day of treatment
34. H. R. 563612 1951 25	Congenital H. D.	Dental extraction	Ductus (postop.)	Recanalization of ductus	P: 0.05 A: 0.05 Ch: 1.5 S: 3.1	P: 6.4 × 40 days A: 2 × 9 days (probenecid)	Survived, prompt response, ductus successfully ligated and divided
35. W. P. 623469 1952 40	R. H. D.	Dental extraction	A M	Heart failure (later)	P: 0.05 A: 0.05 T: 0.19 E: 0.09	P: 20 × 42 days S: 2 × 14 days A: 4 × 35 days (probenecid)	Survived; infection cleared, but serious valve damage; died in failure 20 mo. later
36. J. T. 276556 1953 20	Congenital H. D.	Pelvis	I-V septum	.....	P: 62.5 E: 2+ (disc) Ch: 2+ (disc)	E: 3.6 × 34 days Ch: 3 × 16 days P: 8 × 35 days (probenecid)	Survived, infection responded only after penicillin was added
37. G. H. 650413 1953 17	R. H. D.	.....	A M	.....	P: 50 E: 3+ (disc) Ch: 2+ (disc) Bac.: 2+ (disc)	P: 24 × 27 days 6-12 × 15 days E: 3.6 × 25 days 4.5 × 24 days	Survived, cultures remained sterile after second day
38. C. A. 317344 1953 39	Lupus erythematosus	Abscess	A M	.....	P: 12.5 S: 1.5 A: 0.38 T: 0.19 E: 2+ (disc)	P: 15-24 × 48 days S: 1 × 14 days E: 3 × 48 days (?) T:	Survived, remarkable response in patient with lupus

* Penicillin in units; others in micrograms. Disc sensitivity tests indicated 1+ to 4+. P, penicillin; A, chlortetracycline; T, oxytetracycline; S, streptomycin; Ch, chloramphenicol; E, erythromycin.

† Penicillin in millions of units; others in grams per day.

sensitive to erythromycin, bacitracin, and chloramphenicol.

The patient was treated with 24,000,000 units of penicillin and erythromycin in doses beginning at 2 gm. per day orally and gradually increased to 4.5 gm. per day. The patient's temperature slowly returned to normal; he began to gain weight and recovered uneventfully after being treated with penicillin for six weeks and erythromycin for eight weeks. The murmurs present on admission were unchanged. No petechiae or embolic phenomena appeared during the hospitalization.

During the period of penicillin and erythromycin therapy, the patient's serum inhibited the infecting Staphylococcus at a serum dilution of 1:16 and later 1:64. The same inhibition was obtained when the serum was incubated with penicillinase. During the period of erythromycin therapy alone, there was inhibition at a dilution of 1:32.

Comment.—This case illustrates the frequently encountered difficulty in establishing the diagnosis of endocarditis in a patient with valvular disease who survives a staphylococcal bacteremia. The persistent bacteremia with no obvious focus other than the valves makes diagnosis clinically certain but unproved. It is important to remember, in view of Case 1, that staphylococcal bacteremia and valvular heart disease can coexist without bacterial endocarditis.

The course prior to admission in this patient could well be called subacute, emphasizing the fact that the Staphylococcus does not always produce an acute ulcerative endocarditis.

The effect of inadequate antibiotic therapy on the bacteremia was clearly demonstrated. The patient had taken oral penicillin and sulfonamides in unknown, but certainly inadequate, doses up to the day of admission. Three blood cultures made on the day of admission did not become positive for seven days. Three blood cultures made on the second day became positive in 24 hours. It is obvious that the antibiotics given prior to admission delayed the growth of the organisms in the cultures. The cultures made 24 hours after the last antibiotic therapy became positive promptly. In this case it was of great value to delay therapy and obtain cultures after suppressive antibiotics had been cleared from the blood.

CASE 3 (J. H. H. 563612).—H. R., a 25-year-old white woman, had a tooth extracted without prophylactic antibiotic therapy approximately seven weeks after ligation of a patent ductus arteriosus. Shortly thereafter she developed chills, low-grade fever, lethargy, anorexia, and headache. After three and one-half weeks of these symptoms, chlortetracycline (Aureomycin) therapy (2 gm. daily by mouth) was begun and was continued for 10 days. Anorexia, malaise, chilly feelings, and fever persisted at the time of admission, in December, 1951.

The temperature was 101.8 F; blood pressure, 110/50, and the patient was in no acute distress on admission. No petechiae or embolic phenomena were noted. In the second interspace to the left of the sternum there was a loud to-and-fro continuous murmur. Blood cultures were positive for a hemolytic M. pyogenes var. albus which was sensitive to penicillin in a concentration of 0.05 units per cc. and was also sensitive to chlortetracycline. The patient was treated with 6,400,000 units of penicillin intramuscularly per day with 2 gm. of probenecid (Benemid) by mouth. There was prompt defervescence, and the treatment was continued for three and one-half weeks, at which time the recanalized patent ductus was divided surgically. Subsequent to operation 2 gm. of chlortetracycline daily was added to the penicillin, and this therapy was continued for three weeks. The patient was known to be in good health three years later.

Comment.—This case, like that of J. T. (Case 4) illustrates the failure of suppressive antibiotics to eradicate the infection even though in the present case the organism was sensitive by in vitro test. Adequate penicillin therapy combined with correction of the anatomical defect resulted in a cure.

CASE 4 (J. H. H. 276556).—J. T., a 20-year-old white girl with a known interventricular septal defect developed fever and chilly sensations two days before admission to the hospital, in December, 1953. Her past history included uterine curettage for menorrhagia three weeks prior to admission. There was a past history of fever following penicillin injections which suggested that the patient might be sensitive to penicillin.

On the day before admission, because of pyuria and fever she was treated with penicillin and sulfadiazine. On admission to the hospital on the following day the temperature was 105 F; no petechial lesions were seen, and a loud harsh systolic murmur and thrill were heard in the third left interspace. The white cell count was 16,800 per cubic millimeter. Cultures of six blood samples drawn during the first 24 hours were positive for hemolytic M. pyogenes var. aureus. The organism was found to be moderately sensitive to erythromycin and

chloramphenicol but relatively resistant to streptomycin, chlortetracycline, bacitracin, oxytetracycline (Terramycin), and carbomycin (Magnamycin). It was resistant to penicillin, being killed by 62.5 units per cubic centimeter. On the third day of hospitalization the patient had a shaking chill; the temperature rose to 106 F, and a petechial lesion appeared on the soft palate. By this time the sensitivities of the organism were known, and therapy was begun with erythromycin, 3.6 gm/day. During the next 24 hours the temperature fell to normal and patient improved clinically. She remained afebrile for nine days on erythromycin alone, and five daily blood cultures remained sterile. However, cultures of blood drawn while the patient was afebrile on the 6th day and 9th day became positive, and on the 10th day the temperature again rose to 106 F. At this time oral administration of erythromycin was replaced by erythromycin intravenously and chloramphenicol was added in doses of 3 gm. a day. There was again a prompt defervescence, blood cultures became sterile, and the patient was asymptomatic for three weeks. At the end of three weeks blood cultures again became positive for staphylococci, even though the patient felt well and her temperature remained normal. The antibiotic sensitivity of the organism at the time of this and the previous relapse were essentially the same as on admission, i. e., penicillin-resistant and erythromycin-sensitive.

Penicillin had been avoided in the initial therapy because of the questionable history of sensitivity, but at this time, during her fifth hospital week, she was started on 8,000,000 units of penicillin with 2 gm. of probenecid, and the chloramphenicol was discontinued. She remained afebrile and began to gain weight, and blood cultures remained sterile. The patient was treated with penicillin, 8,000,000 units a day; probenecid, 2 gm. a day, and erythromycin, 3.6 gm. a day, for five weeks. No untoward effects of penicillin therapy developed. She remained in the hospital for 10 days after therapy was discontinued and had neither a return of fever nor positive blood cultures.

The serum inhibition studies during the three different therapeutic periods are of interest. During the first period, of erythromycin alone, the patient's organism was killed by her serum in a dilution of 1:4 and inhibited at 1:8.§ During a period in which the patient received chloramphenicol 3 gm. per day and erythromycin 1 gm. per day the serum killed the organism only at a level of 1:1. During the last phase, while the patient was given penicillin and erythromycin, the serum was lethal to the organism at 1:64 dilution, which fell to 1:32 after penicillinase was added.

Comment.—Clinical appearances were misleading in this case. Blood cultures were positive when the patient was afebrile and asymptomatic. Daily blood cultures provided proof that therapy with the bacteriostatic antibiotics was inadequate.

In this patient there was no correlation between in vitro and in vivo effect of the antibiotics. Penicillin, apparently totally ineffective by in vitro test, appeared to be responsible for the clinical cure. In this case, the combination of large doses of penicillin with erythromycin seemed to be the most effective therapeutic program.

Case 5 (J. H. H. 662115).—M. S., a 56-year-old white woman, was referred to this hospital in December, 1953, with the diagnosis of acute disseminated lupus erythematosus. Two months prior to admission she had noted the relatively acute onset of malaise, dry cough, weakness, and anorexia. She developed an intermittent fever to 103 and 104 F, which did not respond to short courses of penicillin, chlortetracycline, and oxytetracycline. Her illness progressed, with the appearance of polyarthralgia, pleuritic pain, hematuria, and mental confusion. The diagnosis of lupus was made, and cortisone therapy was begun, 400 mg. per day, tapering to 100 mg. per day, which she took for 17 days. During the 10 days prior to admission she had several shaking chills.

On admission she was an acutely ill woman with a temperature of 102.6 F. Petechial hemorrhages were present, and fluid was noted in the knees. The only cardiac abnormality was a blowing systolic murmur, loudest in the third and fourth left interspaces at the sternal border. The liver and spleen were not enlarged. The white cell count was 13,000 to 23,000.

Hemolytic staphylococci were cultured from the urine, nasopharynx, and blood. The organism was sensitive to penicillin, chlortetracycline, and oxytetracycline and slightly less sensitive to erythromycin. Therapy was begun immediately with a total of 16,000,000 units of penicillin (i. v. and i. m.), 2 gm. of erythromycin, and 2 gm. of probenecid daily. The serum antibacterial level was found to be lethal for the specific Staphylococcus strain at a dilution of 1:4000, dropping to 1:32 with penicillinase. Temperature fell to normal with therapy, and blood cultures became sterile. Blood for culture drawn on the eighth day was again positive. This Staphylococcus was still sensitive to penicillin and

§ In this and all similar reports the bactericidal level of the serum is recorded as the highest dilution at which there is no growth of the specific Staphylococcus on subculture. The level of inhibition is the highest dilution at which there is evidence of suppression of growth both grossly and on subculture after 24 hours of incubation.

other antibiotics. The erythromycin dosage was raised to 3 gm/day. During the third hospital week massive gastrointestinal bleeding developed, possibly from a cortisone-induced ulcer. The cortisone had been continued after admission because of the danger of withdrawal. The patient became jaundiced, developed convulsions, and died on the 25th hospital day.

Autopsy revealed a small interventricular septal defect with a bacterial vegetation extending from the defect onto the tricuspid valve. There were many septic infarcts in the lung and brain. There were several acute duodenal ulcers, with evidence of recent gastrointestinal hemorrhage.

Comment.—In this case treatment failed despite the sensitivity of the organism to the antibiotics and the presence of a high level of serum inhibition. Inadequate therapy had been given for two months, and multiple abscesses had developed. The administration of cortisone may have been another factor which contributed to the failure of treatment in this case.

CASE 6 (623469).—W. P., a 40-year-old white man, was admitted in November, 1952, because of fever and chills of 24 hours' duration. He was not known to have had acute rheumatic fever or previous heart disease. Nineteen days before admission the patient had had a tooth extracted, with subsequent local pain and swelling. Three days before admission he stuck his finger with a needle and the site became painful. The day before admission he felt perfectly well but suddenly became chilly, weak, and sweaty. He was referred immediately to this hospital.

On admission there was high fever and multiple petechiae. The heart was enlarged. Systolic murmurs consistant with aortic stenosis and mitral insufficiency were present, but no diastolic murmurs could be heard. The blood pressure was 110/70. Several blood cultures were positive for M. pyogenes var. aureus, sensitive to all antibiotics tested. The organism was killed by penicillin at a concentration of 0.05 units per cubic centimeter. Therapy was started immediately, and the patient was treated for six weeks with 20,000,000 units of penicillin intramuscularly, 4 gm. of chlortetracycline, and 2 gm. of streptomycin daily. There was a defervescence from levels of 105 to 106 F down to 101 to 102 F within 24 hours, and the patient was symptomatically improved. After two weeks there was complete defervescence, and the treatment was continued for an additional four weeks. Two weeks after admission to the hospital, an aortic diastolic murmur was heard for the first time. At the time of discharge, blood pressure was 110/80. For the next 20 months the patient was followed very closely and returned to work as a tailor. There was no fever; the white blood cell count remained normal, and occasional blood cultures were sterile. The diastolic blood pressure gradually fell to a level of 50, and the systolic pressure rose to a level of 150. The aortic diastolic murmur became increasingly intense during this period. He began to have occasional anginal pains relieved by glyceryl trinitrate (nitroglycerine). Four months before the second admission, the patient began to lose weight and intermittently would accumulate edema fluid and become short of breath. Twenty months after his first admission he was readmitted in severe heart failure. There was no clinical or laboratory evidence of bacterial endocarditis. After admission, the patient had repeated pulmonary infarctions and finally died of a large pulmonary embolus. At autopsy, there was a healed bacterial endocarditis of the aortic valve, with very marked aortic stenosis and insufficiency. There were multiple pulmonary infarctions.

Comment.—This patient illustrates the unfortunate fact that even with a penicillin-sensitive Staphylococcus and prompt, adequate therapy the valve may be irreparably damaged.

GENERAL COMMENT

A review of the clinical picture and therapy in the 38 cases of staphylococcal endocarditis reveals certain points that seem worthy of emphasis.

As mentioned earlier, the diagnosis of acute bacterial endocarditis may be a difficult one to establish. For instance, in our case reports we have referred to a patient (Case 1) with known valvular disease, in whom staphylococcal septicemia of several days' duration was followed by death without any evidence at autopsy of bacterial endocarditis. Knowledge of this case makes one hesitant to make the diagnosis of endocarditis on the basis of septicemia and a murmur alone. There were four additional cases of staphylococcal septicemia and valvular heart disease without sufficient clinical evidence of bacterial endocarditis. However, these patients all survived, and there is no autopsy proof of the absence of bacterial endocarditis.

The onset and course at times may simulate the subacute form of the disease rather than the fulminating course usually associated with this organism. Case 2 gives an

example of this variation of the clinical picture. This patient's symptoms were mild and started two weeks before admission. He was not acutely ill; the temperature was only slightly elevated, and the white blood cell count was normal. This is known to occur occasionally, being described in 4 of 26 cases of M. pyogenes var. aureus endocarditis reported by Thayer in 1926.[14] In our series, five cases presented a subacute course of one month or more before admission.

There are other features which may shake our faith in some of the usual diagnostic criteria. For example, the white blood cell count may at times be misleading, for, though the majority have a leucocytosis, the count is sometimes normal or even low. In our group the white cell count was elevated in most cases, but in 5 of the 38 it was from 5000 to 10,000. The diagnosis is difficult to make without definite evidence of heart disease. Our Case 5 presented this problem and was found to have a patent interventricular septal defect evidenced only by a blowing systolic murmur which might easily have been considered insignificant.

Another point worth noting is that previous antibiotic therapy may suppress the growth of the bacteria enough so that the first blood cultures may either remain sterile or show delayed growth. This was true of one of our patients who had received penicillin before admission. In this boy (Case 2) the cultures taken on the day of admission did not become positive for seven days, whereas those taken the second day grew out in 24 hours. These are examples of some of the pitfalls we may encounter in trying to establish this diagnosis and evaluate therapy. Therefore, though we have tried in this series to include only those cases that were either pathologically proved or seemed clinically certain, in one or two of the latter the accuracy of the diagnosis of bacterial endocarditis might be questioned.

The danger of concomitant or prior therapy with cortisone was pointed out in our Case 5 and in another—a patient with ulcerative colitis who had received corticotropin (ACTH); this may have played a role in the fatal outcome. The adverse effect of cortisone on the course of many infections is well recognized; it may be even more of a hazard in a fulminating staphylococcal infection, whether or not the organism is sensitive to antibiotics.

Just as has been stressed repeatedly in subacute bacterial endocarditis, though the infection may be eradicated, there remains the danger of extensive valve damage followed by myocardial failure. Such was the case in three of our patients, in one of whom heart failure developed during treatment and was a contributory cause of death. One of the survivors was in myocardial failure at the time of discharge, and the third (Case 6) died of this complication more than one an one-half years after the valve infection had been promptly and successfully treated. Examples such as these point up the urgent need for prompt diagnosis and treatment; the longer the bacterial focus remains active, the more likely is the function of the involved valve to become seriously impaired.

An interesting and unexpected finding was that the majority of strains studied in the last five-year period were sensitive to penicillin. Thus, of 12 on which this test was performed, 7 were killed by less than 1 unit per cubic centimeter. One of these was sensitive to as low a concentration as 0.03 unit, and three to 0.05 unit per cc. The remaining five, therefore, or 42%, were resistant to 1 unit or more, the values being 1.9, 12.5, 50, 62.5, and 250 units per cubic centimeter. The number of cases is, of course, too small to warrant any conclusion, but the results are at variance with reports from some other areas. For instance, in several clinics referred to earlier‖ approximately 70% of the staphylococci were penicillin-resistant. Spink, in 1954,[4] reported that 60% of a group of septicemias had organisms resistant to as much as 50 units per cubic centimeter. In a series of 25 cases of staphylococcal endocarditis reported by Dowling and others in 1952,[15] 48% of the strains were resistant to 1 unit per cubic centimeter or

‖ References 1-3.

more; of those whose organisms were sensitive to penicillin there were 9 recoveries, thus indicating the relatively favorable prognosis of patients in this category.

In our seven patients with sensitive strains referred to above, there were four survivals and three deaths. Two of the latter were receiving corticotropin or cortisone, and the other was the patient who died with heart failure and continued activity of the infection. Two of the five whose infections were due to resistant strains died. One of these was a 10-year-old boy, whose organism was extremely resistant, being killed only by 250 units of penicillin. After an unsuccessful trial of 12,000,000 to 24,000,000 units of this antibiotic per day, the infection seemed under control when other drugs were substituted, but it recurred three days before death. In another fatal case, the organism was only slightly resistant to penicillin, being killed by 1.9 units, although the strain was considered to be resistant by the disc technique. The infection had been suppressed temporarily by a course of chlortetracycline given in another hospital. The organism had been reported as sensitive to chloramphenicol, and that antibiotic was employed for the three remaining days of the patient's life, without any obvious effect on the course. Tests performed by tube dilutions indicated that a combination of large doses of penicillin with either chlortetracycline or oxytetracycline would have been preferable. On the basis of this case, as well as one other in which the strain was classified as resistant by the disc test but was found to be reasonably sensitive by the tube-dilution method, we feel strongly that the disc method should not be relied on to the exclusion of more exact methods in any patient with staphylococcal bacteremia or endocarditis.

The three who survived are of especial interest, because, though their organisms were resistant to less than 12.5, 62.5, and 50 units of penicillin, massive amounts of that agent combined with large doses of erythromycin led to a favorable outcome in each. In one of these patients (Case 4) penicillin was withheld for a period because of a history suggesting sensitivity to that drug. During erythromycin and chloramphenicol therapy the blood cultures again became positive and there was clinical relapse. Penicillin was then added, with a prompt response and final cure of the infection. Another example is Case 2, a boy with rheumatic heart disease whose organism was killed only by 50 units of penicillin per cubic centimeter. This patient also responded well to penicillin and erythromycin, the course being continued for more than six weeks. Examples such as these make us feel that, regardless of the laboratory findings, the therapeutic regimen should include massive doses of penicillin. One reason for this choice is that penicillin can be given in almost unlimited amounts, and another is that it is primarily bactericidal. It should be used in combination with one or more of the antibiotics which may show greater in vitro activity but which are bacteriostatic in action. This is similar to the experience of others in the treatment of subacute bacterial endocarditis.¶ In the present study, no patient was cured by any combination of antibiotics which did not include penicillin. We have not used bacitracin in any of these patients, but others who have had experience with it recommend it in penicillin-resistant cases, usually in combination with one of the bacteriostatic drugs.#

In several of the patients an "antibacterial serum test" was employed as an additional guide to therapy. In this test serial dilutions of the patient's serum are made in broth and the same inoculum of the specific Staphylococcus added to each. Determinations could then be made of the levels of bactericidal and bacteriostatic activity in the blood at any time during the course of therapy. This seemed to help in some cases. In some patients a parallel series was run in which the penicillin in the serum was neutralized with penicillinase. Even in those found resistant in vitro the test usually indicated that penicillin was contributing to the antibacterial effect.

¶ References 5-8.

References 4, 13, and 16.

Other features of the clinical problem presented by this group of 38 patients are worth summarizing, though some question can always be raised regarding any findings not proved by autopsy (Table 4). Of those having preexisting valvular heart disease the lesions were considered to be congenital in 10 and rheumatic in 9. The relative incidence of rheumatic and congenital lesions was six to two in the autopsy-proved group as opposed to four to seven in the so-called clinically certain group. That a staphylococcal bacteremia can occur in the presence of valvular disease without endocardial vegetation has been clearly shown in Case 1. In this small series, the most frequent congenital lesion was the interventricular septal defect, and three of the autopsy-proved cases presented an almost identical picture, with the vegetation arising in the septal defect and extending onto the adjacent tricuspid valve.

TABLE 4.—*Data on Types of Endocardial Involvement**

	Class I	Class II	Total
I. Preexisting heart disease			
Congenital	6	4	10
Rheumatic	2	7	9
Hypertensive arteriosclerotic	6	0	6
II. Site of vegetation with preexisting endocardial disease			
A. Rheumatic heart disease			
Mitral valve	2	5	7
Aortic valve	0	3	3
B. Healed streptococcal endocarditis	0	1	1
C. Congenital			
Aortic, bicuspid	1	0	1
Patent ductus	1	2	3
Blalock anastomosis	1	0	1
Pulmonic stenosis	1	0	1
I-V septal defect	3	1	4
III. Site of vegetation with no preexisting heart disease			
Mitral valve	12	0	12
Tricuspid valve	8	0	8
Aortic valve	2	3	5
Ventricular wall	2	0	2

* Class I, autopsy proved. Class II, clinically certain.

In the first 10-year period there were 22 cases, with 1 survivor. This was a 23-year-old patient with a patent ductus who had a prolonged, subacute type of course and was improved after four weeks therapy with sufanilamide, antiserum, and transfusions. In the five-year period from 1944 to 1949 there were two deaths and one recovery. Most of the findings in the last group of 13 have been dealt with in the preceding discussion. Of these, there was a recovery rate of 54%.

On the basis of this experience, we feel that the most effectual therapy for staphylococcal endocarditis at the present time is a combination of penicillin, erythromycin, and one of the "broad-spectrum" antibiotics. One is guided in this selection to some extent by sensitivity tests and also by serum tests during therapy, but penicillin should always be included, even when the organism is resistant by laboratory tests. Massive doses are advocated, namely 8,000,000 to 24,000,000 units a day, depending on the sensitivity. Large doses of erythromycin can be given, as one of our patients took 3.6 gm. per day for 5 weeks and another, 3.6 gm. for 25 days and 4.5 for an additional 24 days without toxic symptoms. This therapy should be instituted as soon as the diagnosis has been suspected and blood cultures taken. If the antibiotics are not given promptly and in effective amounts there is danger of the development of antibiotic resistance, as has been found with penicillin * and erythromycin.† It is interesting, however, that in two of our patients in whom the blood cultures reverted to positive again during treatment the sensitivities of the organisms showed no essential change.

Another complication that is apt to occur if the treatment is delayed is the formation of multiple abscesses and infected infarcts in various organs. In these areas the bacteria may be walled off and difficult to reach with any of the drugs. That was shown at autopsy to be true in at least four of our patients (Cases 27, 28, 29, and 31) and must have contributed to their unfavorable response. It is hard to be exact as regards duration of treatment, but most of our successful cases were treated for six or seven weeks, and we would hesitate in a condition as serious as this to advocate stopping any sooner.

* References 1-4.

† References 9-13.

SUMMARY

The high incidence of antibiotic-resistant strains represents one of the major problems in the therapy of staphylococcal infections at the present time.

Some of the diagnostic criteria for staphylococcal endocarditis are evaluated and discussed.

Data have been reviewed on 38 cases of staphylococcal endocarditis. Thirteen of these were seen during the five-year period from 1949 through 1953.

The incidence of penicillin-resistance in this last group was 42%. The survival rate was 54%.

Recovery showed no definite correlation with sensitivity of the Staphylococcus to penicillin. It seemed dependent, however, on the administration of massive doses of that agent with erythromycin or other antibiotics, irrespective of the results of in vitro tests for penicillin sensitivity.

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Hereditary Ovalocytosis (Elliptocytosis) with Hypersplenism

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Oval or elliptically shaped erythrocytes normally occur in the camel and llama but are comparatively unusual as a hereditary trait in the human.* While the phenomenon is said to have been observed by Goltz † as early as 1860, it was first reported by Dresbach ‡ (1904) and later firmly established as a hereditary anomaly by Bishop [4] (1914) and by Hunter and Adams [5] (1929). A number of interesting presentations are included in the approximately 60 reports which have accumulated in the medical literature since Dresbach's original papers. Of these, the reports and discussions of Lambrecht,[1] Gunther,[6] Leitner,[7] Wyandt and co-workers,[8] and, most recently, Guasch and Raichs [9] are especially informative. The limitations of pure morphology and of morphological description and classification of blood cells make it impossible to evaluate critically all the reported cases, but it appears that between 350 and 400 cases of this anomaly have been reported. Of these, it is estimated that only about 12% exhibit a significant anemia,[10] and many authors stress the fact that the anomaly is usually not associated with anemia or any other hematologic abnormality. However, the data presented in some of the reports suggest that substantially more than 12% of cases have an increased rate of red cell destruction, which is usually compensated by an increased rate of erthropoiesis. Vischer, who first observed a shortened red cell survival in this anomaly, pointed out that this was usually compensated by increased erythropoiesis unless infection or hypersplenism disturbed this equilibrium.[11] This view has been supported by others who, with Vischer, place this anomaly, with hereditary spherocytosis and the sickling phenomenon, in the group of hemolytic anemias due to erythrocyte defect.§

The incidence of splenomegaly in persons with this anomaly is very uncertain, since many of the patients reported in the larger series apparently have been subjected to blood study only. However, splenomegaly in hereditary elliptocytic anemia has been observed by numerous workers,‖ and splenectomy has been performed in eight cases, including the one presented here.¶

The two patients being reported here are of interest because both exhibited significant anemia and splenomegaly and one of these underwent splenectomy, with a remarkable clinical and hematologic response. These are two of five siblings whose parents are dead. Of the two brothers and three sisters in the family, one brother and one sister exhibited ovalocytosis with anemia. The other three siblings do not show the trait, and all five siblings are childless. There are no known living relatives.

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* The terms "ovalocytosis" and "elliptocytosis" are used synonymously as applied to the hereditary anomaly characterized by the presence of large numbers of ovoid and elliptical erythrocytes.

† Cited by Lambrecht.[1]

‡ References 2 and 3.

§ References 12 and 13.

‖ References 9 and 12 to 21.

¶ References 9 and 17 to 21.

CASE 1.—T. T., a 63-year-old single white woman, was admitted to Chicago Wesley Memorial Hospital, with chief complaints of abdominal pain on two occasions. She stated that for some years she had had a "low blood count" and had been receiving liver injections for what was thought to be pernicious anemia. She had otherwise been well until six weeks prior to admission, when she first experienced colicky upper abdominal pain without nausea or vomiting. This attack subsided after several days of bed rest and antibiotic therapy. Cholecystography subsequently failed to visualize the gall bladder. Six weeks later there occurred a second attack of colicky and cramping epigastric pain, which radiated around the right costal margin and up to the scapula. The urine became dark, and the patient became moderately jaundiced.

The past history was not significant; menopause occurred at 47 years.

The family history was noncontributory, except for the second case to be described. Both parents lived to very advanced old age, and there was no family history suggestive of anemia.

Physical examination revealed a temperature of 100.2 F and moderate icterus. The liver was enlarged 3 cm. below the costal margin in the midclavicular line and was slightly tender. The spleen was enlarged 3 cm. below the costal margin in the anterior axillary line and was firm and nontender. The blood pressure was 160/90. Physical findings were otherwise not remarkable.

The peripheral blood picture was as follows: erythrocytes, 2,750,000 per cubic millimeter; hemoglobin, 9.0 gm. per 100 cc.; leucocytes, 4200 per cubic millimeter, with neutrophiles 68%, lymphocytes 18%, monocytes 14%, blood platelets 360,000 per cubic millimeter, reticulocytes 1.0%. The leucocytes were morphologically normal, but over 80% of the erythrocytes were oval or elliptical (Fig. 3*A*). There were a few microcytes and microspherocytes. The urine contained bile but was otherwise normal. Total serum bilirubin was 2.2 mg. per 100 cc.

The patient was given supportive therapy and antibiotics, and in three days the fever had subsided. Two days after admission the total serum bilirubin was 1.2 mg. per 100 cc. Liver-function studies were undertaken at this time; serum proteins, prothrombin, alkaline phosphatase, and cephalin flocculation were all normal. Fecal urobilinogen on a single specimen was 1223 mg. per 100 gm. of feces.

Repeat peripheral blood studies one and two days after admission were similar to the initial observation. Saline osmotic fragility of the erythrocytes was normal at this time (Fig. 2). Coombs's test was negative. Paper electrophoresis and standard Tiselius electrophoresis (carried out in 1954, after splenectomy) showed a motility pattern of normal (A) hemoglobin.# Alkali denaturation revealed 1.4% fetal hemoglobin.* Sternal marrow study revealed hyperplasia of all cellular elements but with relative erythroid hyperplasia and a moderate erythroid left shift. A few of the normoblasts were slightly but definitely ovoid; all other nucleated erythroid elements were normal in shape.

An epinephrine (Adrenalin) test was done on July 19, 1951. A bounding pulse, epigastric pulsation, and moderate rise in systolic blood pressure after intramuscular injection of 0.6 cc. of 1:1000 epinephrine was evidence of a satisfactory systemic response to the drug. The hematologic response to epinephrine is presented in Figure 1. The total leucocyte count rose from 5100 to 22,880 per cubic millimeter, with a proportionate increase in granulocytes and lymphocytes. The erythrocytes increased from 3,000,000 to 4,600,000 per cubic millimeter, and the reticulocytes, from 2.4% to 10.6% (from 72,000 to 430,000 per cubic millimeter). Platelets increased from 120,000 to 330,000 per cubic millimeter (Rees-Ecker). This response was considered a positive test and was interpreted as indicating splenic hypersequestration of all types of blood cells.

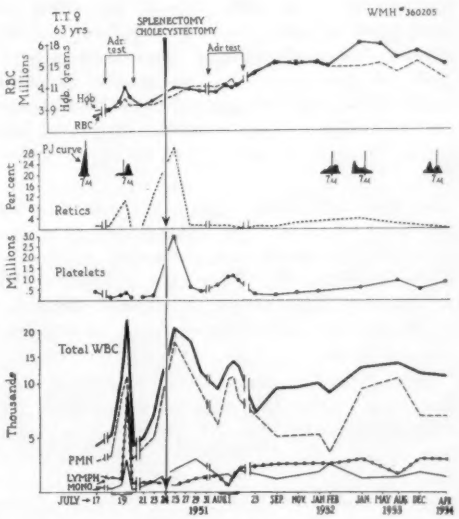

Fig. 1.—Ovalocytosis with hypersplenism.

On July 24, 1951, a cholecystectomy with exploration of the common bile duct and splenectomy with exploration for accessory spleens was performed by Dr. T. Howard Clarke. The gall bladder showed evidence of chronic inflammation and contained 12

Dr. Karl Singer made these determinations, which were done, after splenectomy, in 1954.

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pigment stones. The spleen, which had been vigorously massaged before removal, weighed 291 gm. On gross inspection the cut surface of the spleen revealed a congested bright red parenchyma with occasional indistinct follicular markings. Microscopic examination revealed marked reticular hyperplasia and dilatation of the sinusoids, which contained comparatively few red cells in contrast to the engorged pulp spaces. Numerous macrophages containing hemosiderin pigment lay along the sinusoidal walls and in the pulp spaces.

The patient was out of bed on the second postoperative day and made an uneventful recovery. Twenty-four hours after splenectomy the reticulocytes had risen to 29.2% (1,190,000 per cubic millimeter), and blood platelets, to 2,980,000 per cubic millimeter (Fig. 1). The marked reticulocytosis was interpreted as indicating an outpouring of sequestered reticulocytes as a result of splenic massage before clamping of the splenic pedicle. The red cell count was moderately increased (3,380,000 to 4,100,000 per cubic millimeter) immediately after surgery; however, the patient had received one unit of whole blood during the operation.

A repeat epinephrine test on the seventh postoperative day showed little change in any of the circulating blood cells except platelets, which rose from 670,000 to 1,100,000 per cubic millimeter. This is less than significant by our criteria. Since recovery from the operation the patient has remained in good health.

During the first six months after splenectomy there was a rapid and progressive increase in red cells and hemoglobin; in the three months between Aug. 1 and Nov. 1, 1951, the erythrocyte count rose from 3,900,000 to 5,100,000 per cubic millimeter, and the hemoglobin, from 10.5 to 15.0 gm. per 100 cc. The reticulocytes and platelets had returned to normal levels soon after surgery. The leucocytes gradually declined postoperatively to fairly constant levels of 7,000 to 12,000 per cubic millimeter, in contrast to the preoperative leucopenia.

During the first two months after splenectomy, when the erythrocyte levels were increasing sharply, we first observed the appearance of large numbers of triangular, elliptical, and spherocytic microcytes. There was a relative and absolute increase in these microcytes for 17 months after splenectomy. This is evident in the second photomicrograph (Fig. 3*B*) and is reflected in the increasing red cell counts in the presence of stationary hemoglobin levels, which became apparent between November, 1951, and January, 1953 (Fig. 1). The phenomenon is also reflected in the alteration of red cell indices and the modified Price-Jones curve in Figure 2. It will be noted that the mean corpuscular volume, mean corpuscular hemoglobin, and, particularly, the mean cell diameter dropped appreciably between July 19,

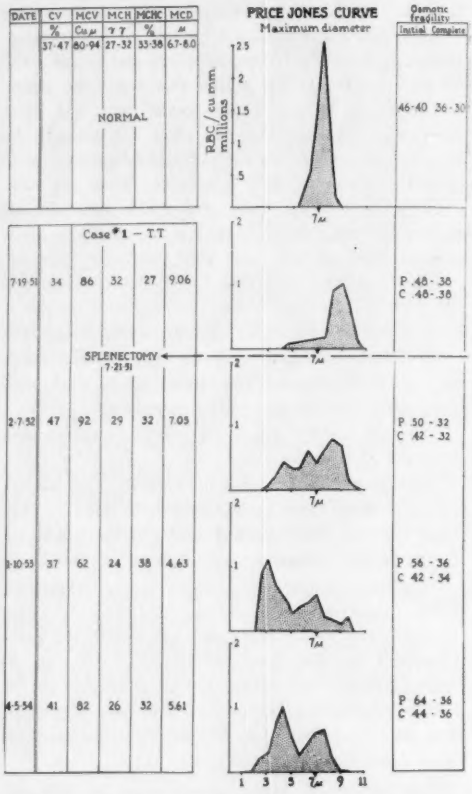

Fig. 2.—Red cell indices, modified Price-Jones curves, and osmotic fragility changes.

1951, and Jan. 10, 1953, and that they tend to increase in the final figures. The modified Price-Jones curves shown in Figure 2 and in miniature silhouette in Figure 1 are based upon the measurements of maximum cell diameters (abscissa), and the measured cells have been graphed in terms of absolute numbers of cells per cubic millimeter (ordinate). It is evident that before splenectomy the great predominance of cells were large ovalocytes and elliptocytes, ranging from 8.0 to 9.5μ in maximum diameter. Following splenectomy there was a progressive increase in microcytes until January, 1953 (17 months after splenectomy). The predominant cells were microspherocytes less than 3μ in maximum diameter; cells greater than 7μ in diameter were very scarce. A dramatic reversal toward the presplenectomy pattern is evident in a curve plotted in April, 1954 (33 months after splenectomy) indicating a distribution of cell size in two fairly well-defined groups, with large (7μ) and smaller (3μ) ovalocytes and elliptocytes reappearing in substantial proportions in two peaks.

However, since May, 1953, the cell volume and mean corpuscular hemoglobin have been reduced, and, as one would expect, this is reflected in the

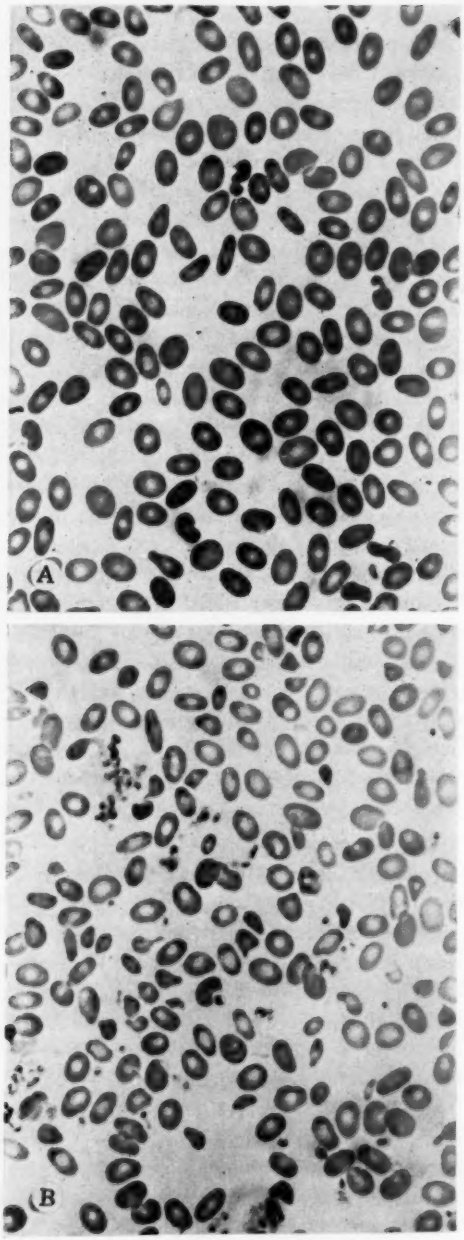

Fig. 3.—*A*, peripheral blood smear before splenectomy; *B*, after splenectomy.

gradual fall in total red cell count and in the lessening discrepancy between red cell and hemoglobin levels. This is consistent with the Price-Jones curve, which shows a shift back to large ovalocytes and away from spherocytic cells. It is also to be noted that there is a modest but consistent fall in both red cell and hemoglobin levels from the highest point reached, six months after splenectomy, until the present time. Thus, for the first six months after splenectomy there was a concomitant rise in red cells and hemoglobin and the appearance of large numbers of microspherocytes and elliptocytes. During the following year there was a continued increase in microcytes and the absolute replacement of larger cells by smaller ones. Finally, during the 16 months after January, 1953, there has been an appreciable fall in red cell count and a slighter decline in hemoglobin levels, reflected in the indices and in the shift back to cells of greater diameter.

As stated previously, the presplenectomy osmotic fragility was normal. However, as one might predict, the appearance of large numbers of microspherocytes, after splenectomy, was associated with an increase in osmotic fragility.

From the time of recovery from surgery the patient insisted that she felt better than at any previous time in her life. Other members of the family stated that she showed color in her cheeks for the first time that they could recall.

Case 2.—J. T., 57 years old, brother of the first patient, was first seen as a patient at the age of 48 by Dr. Thomas J. Coogan, who made available all of his records for this study. At the time of the first admission to St. Luke's Hospital, Chicago (1942), the findings were consistent with healed rheumatic heart disease in congestive failure and bronchiectasis of the right lower lobe. A single blood cell count was normal, and no red cell morphology observations were recorded. Three years later, at the age of 51, the patient was readmitted to St. Luke's Hospital with spontaneous pneumothorax thought to be due to rupture of an emphysematous bleb. Again, cardiac findings were those of healed rheumatic heart disease with mitral stenosis. At that time a blood study showed erythrocytes 3,600,000 per cubic millimeter, with 10.5 gm. of hemoglobin per 100 cc., and 10,650 leucocytes per cubic millimeter, with a normal differential count. Ovalocytosis "3+" was noted at this time. He was again admitted to the hospital three years later, at the age of 54 years, and on this admission the red cell count was 2,100,000 per cubic millimeter; hemoglobin, 9.3 gm. per 100 cc., and hematocrit value, 30.0%. A "large percentage" of ovalocytes was noted in the blood smear at this time. In January, 1949, at the age of 55, the patient was studied at a clinic. Peripheral blood picture at this time showed an erythrocyte count of 3,850,000 per cubic millimeter, hemoglobin 10.8 gm., and hematocrit value 30.5%. The direct bilirubin was 0.7 mg. and total bilirubin 1.1 mg. per 100 cc. No hematologic diagnosis was recorded.

The discovery of the nature of the sister's anemia as recounted here and our resulting interest in carrying out intensive blood studies in this patient

increased his usual suspiciousness of character and greatly limited the scope of our investigation. However, physical examination and x-ray study established the fact of marked splenomegaly as well as moderate hepatomegaly. Repeat peripheral blood studies showed erythrocyte counts ranging from 3,600,000 to 3,790,000 per cubic millimeter, hemoglobin from 10.3 to 12.5 gm. per 100 cc., reticulocytes from 6.8% to 12.2%, and leucocytes from 8,000 to 10,500 per cubic millimeter. Osmotic fragility was normal. The patient refused splenectomy. He was readmitted to St. Luke's Hospital in December, 1952, in congestive heart failure and died.

Autopsy was performed by Dr. Edwin F. Hirsch. Autopsy findings were healed rheumatic heart disease with mitral stenosis, pulmonary congestion and fibrosis, slight enlargement of the liver with moderate passive congestion, erythroid hyperplasia of the bone marrow, and marked splenomegaly. The spleen weighed 640 gm. Microscopic examination showed reticular hyperplasia and fibrosis, with congestion of the pulp spaces and dilatation of the pulp spaces and sinusoides. There was marked hemosiderin deposition in both the spleen and the liver.

The second patient declined complete study and splenectomy, but there are enough data and genetic circumstance to consider these two cases as being hematologically similar. The red cell morphology, normal (preoperative) osmotic fragility, degree of anemia and of reticulocytosis, bone marrow hyperplasia, and the size and degree of reticular hyperplasia and hemosiderosis of the spleen are comparable in these two patients. These facts, together with the response to splenectomy in Case 1, seem to be a reasonable basis for a presumption of splenic hypersequestration in Case 2 as well.

COMMENT

As previously noted, morphological description alone leaves much to be desired in classifying erythrocyte abnormalities of any kind. An appreciable percentage of oval and elliptical erythrocytes is probably seen most commonly in anemias secondary to neoplastic bone marrow invasion, severe chronic blood loss, and hypoplastic states, but they are also fairly common in nutritional deficiency anemia, especially pernicious anemia. In an attempt to circumvent confusion in identification and classification of this hereditary anomaly with ovalocytes, elaborate systems of measurement and classification have been developed. Of these the most remarkable is the one set forth by Guash and Raichs.[9] Gunther [6] developed four categories of cells (circle, circle-like, elliptic, and small elliptic), which were based on measurements of width and length. The percentile distribution into the various categories was the basis for identification of this anomaly. This classification pervades the literature and was the basis for description of many subsequently reported cases. It has been noted that demonstration of a familial relationship in the anomaly is the best evidence that the abnormality is not one of the acquired types of poikilocytosis referred to above. Even here, however, there may be confusion. Pontoni's review [22] and case reports and Fanconi's case [23] are illustrative of the fact that it may be difficult to separate hereditary elliptocytosis from thalassemia and other hereditary erythrocyte defects even when studies of patients' families supplement hematologic findings. Elliptocytosis has been reported in a patient with sicklemia,[24] and a substantial number of the apparently bona fide cases of ovalocytosis, including the first reported case of Dresbach, have been in Negroes.

In the report of their study on elliptocyte survival, Motulsky and co-workers [25] discuss the relationship of hereditary elliptocytosis to other hereditary hemolytic syndromes and recall the fact that electrophoretic investigations of genetically determined hemoglobin abnormalities are clarifying our understanding of the widely varying picture presented by thalassemia and sicklemia. They point out that electrophoretic studies of their seven cases of nonhemolytic elliptocytosis showed normal (A) hemoglobin. Motulsky and coworkers draw an analogy from thalassemia and suggest that the occurrence of increased hemolysis may depend on whether the inheritance of the trait is heterozygous or homozygous. They also suggest that when elliptocytic anemia occurs in a known heterozygous inheritance there may be genetic combinations of other abnormal hemoglobins, as in sickle cell-hemoglobin C anemia. A genetic study was not possible in the cases

presented here. However, alkali denaturation [26] and hemoglobin electrophoresis of Case 1 established this as a normal (A) pattern and support our impression of uncomplicated hereditary ovalocytosis. These data also indicate that this hereditary abnormality is a defect in the ultrastructure of the red cell rather than a hemoglobinopathy.

Role of Spleen in Ovalocytic Anemia.—The cases of ovalocytosis in which splenectomy has been done emphasize the parallelism between this anomaly and congenital hemolytic icterus, though the normal preoperative osmotic fragility studies as well as the morphological differences should leave no doubt as to the distinctiveness of the two entities. In both diseases we are dealing with an abnormality of erythrocyte formation which ultimately results in hyperactivity and reticular hyperplasia of the spleen. In a certain number of cases the increased red cell destruction (shortened survival) is so great that the bone marrow production cannot compensate and anemia results. Removal of the spleen results in recovery from the anemia without altering the hereditary red cell defect. In one of the cases reported here and in those of Holst-Larsen [19] and Dacie and co-workers,[20] splenectomy resulted in the appearance of many microcytes of various shapes, particularly microspherocytes. The presence of these cells implies fragmentation of erythrocytes, and their sudden increase following splenectomy suggests one or both of the following explanations: 1. The spleen had an inhibitory effect on the production of easily fragmented cells. 2. Hypersequestration by the spleen was responsible for a shortened survival of all erythrocytes as well as for a relatively rapid removal of microcytes from the circulation. Splenectomy resulted in a prolonged red cell survival with a greater degree of fragmentation and without the prompt removal of the resulting fragments.

Björkman's Hypothesis.—In his studies of splenic circulation, Björkman [27] devised a unique experiment in which rice starch granules of various sizes were injected into the venous circulation of the rabbit and their distribution was studied after death. He observed that the greatest number of granules were in the splenic pulp cords. Furthermore, a high percentage of small granules were trapped in the pulp cords, whereas a large percentage of larger granules were retained in the sinuses. These findings support the observations of Knisley [28] and are consistent with Björkman's findings in tissue studies of the spleen in the human. Björkman's observations on the method and site of sequestration of the various sizes of rice granules offer an excellent explanation of the cytological changes in these two cases of ovalocytosis and in those of Holst-Larsen and Dacie and co-workers. The salient features (Fig. 4) indicate that in the deplasmatization phase of splenic sinus filtration the fragmented microcytes were filtered into the pulp spaces, where they were phagocytized. The larger cells were retained in the sinus spaces, to be returned to the general circulation after the deplasmatization phase of filtration. The removal of the spleen not only removed the filter but resulted in a sufficiently increased red cell survival that extensive fragmentation occurred and continued without prompt removal of the fragments. The more recent reduction in the circulating microcytes may reflect a compensatory hyperplasia of other reticuloendothelial elements.

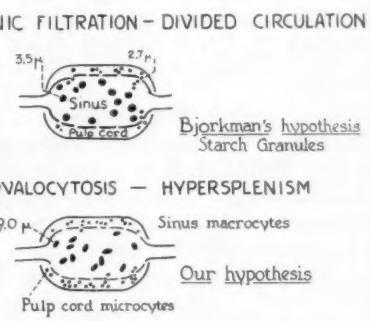

Figure 4.

SUMMARY

Two cases of hereditary ovalocytosis are presented. These siblings exhibited pancytopenia, splenomegaly, and bone marrow

hyperplasia. One patient underwent splenectomy, with recovery from the pancytopenia. However, numerous microcytes of various shapes appeared in the peripheral blood. Björkman's hypothesis of a divided splenic circulation seems a plausible explanation for the cytological picture preceding and following splenectomy.

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Renal Biopsy in Pyelonephritis

Correlative Study of Kidney Morphology, Bacteriology, and Function in Patients with Chronic Urinary Infections

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Infections of the urinary tract are protean in their clinical manifestations, pathogenesis, and pathologic importance as well as in bacterial etiology. A few reports differentiating chronic pyelonephritis from Bright's disease * appeared in the literature prior to 1939, but, in general, until recently, clinical infections of the urinary tract were classified according to the anatomic part believed to be the site of the infection. Thus, urethritis, cystitis, pyelitis, and pyelonephritis, at least, were regarded as separate entities. The classic publication of Weiss and Parker,[4] in 1939, and others since that time, altered this point of view and indicated a tendency for infection to involve the entire urinary tract regardless of the site of origin of the infection.

Weiss and Parker [4] classified pyelonephritis according to morphologic changes in the kidney into acute, chronic, healed, and healed and recurrent stages. Clinical recognition of acute pyelonephritis is not difficult, but patients with chronic pyelonephritis, as noted by Mansfield, Mallory, and Ellis,[5] rarely give a history of acute pyelitis. Consequently, the evaluation of the renal damage associated with chronic bacteriuria and pyuria in a patient with few symptoms and the recognition of healed pyelonephritis in a patient with renal failure are uncertain when they depend upon the usual clinical methods.

Acute pyelonephritis usually can be treated successfully with antibiotics, but chronic urinary tract infections are among the most difficult of all infections to cure with antibiotics. Such infections and the associated renal damage are often the lethal complication of a metabolic disorder or of minor conditions that obstruct or impede the urine flow. The incidence of pyelonephritis in a recent analysis of 2579 consecutive autopsies since 1939 at the Research and Educational Hospitals was 10.5% among adults, and in one-third of these cases the renal lesion was of major pathologic importance in causing death.[6]

Weiss and Parker [4] also observed that chronic and healed pyelonephritis were commoner than glomerulonephritis, and they estimated that pyelonephritis was responsible for at least 15% to 20% of the cases of malignant hypertension. It has been estimated that one-sixth of the patients with chronic pyelonephritis die with hypertension.[7] Avendaño and co-workers [8] recently observed chronic pyelonephritis in more than 40% of a small group of patients with arterial hypertension, and treatment with antibiotics was claimed to eliminate the hypertension in 10 of 18 such patients. Thus, with the presently available antibiotics and chemotherapeutic agents, it has seemed to us more important than ever before to extend our understanding of the role of chronic, relatively asymptomatic infections of the urinary tract in the pathogenesis of pyelonephritis.

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* References 1-3.

In 1951, Iversen and Brun [9] published a technique for aspiration biopsy of the kidney and subsequently reported their experience in the use of biopsies to study certain diseases involving the kidney.† In the United States, Parrish and Howe [12] have employed a similar technique as an aid in the diagnosis of renal disease. A few patients with pyelonephritis are noted in these reports.

Another significant advance made within recent years has been the development of methods for quantitative measurement of certain kidney functions by Goldring and Chasis [13] and by Smith.[7] The utilization of these methods in the investigation of pyelonephritis has not been extensive.

In the present study of the pathogenesis of pyelonephritis, an attempt has been made to correlate the clinical, bacteriologic, morphologic, and functional status of the kidneys by employing some of these presently available techniques in patients with chronic urinary tract infections. Representative case histories of patients with persistently infected urine are classified on the basis of differences in morphology and function of the kidneys.

METHODS

The patients observed in these investigations were selected from the wards and outpatient department of the Research and Educational Hospitals of the University of Illinois College of Medicine. All the patients were admitted to the hospital for evaluation of their clinical condition as well as for renal biopsy and the measurement of kidney function.

Urinalysis and bacterial cultures were performed on at least four morning samples of urine that were obtained as clean-voided or catheterized specimens. Microscopic analysis was performed upon sediment from 15 ml. of urine after centrifugation at 3000 to 4000 rpm for five minutes, and the sediment was resuspended in 0.5 ml. of the urine. The microscopic findings were reported as an average number of elements per high-power field (× 430). The sediment also was smeared, and after heat fixation it was Gram-stained and examined for bacteria. The remaining sediment was supravitally stained by the method of Sternheimer and Malbin [14] and microscopically examined.

Bacterial cultures were performed on an aliquot of each urine specimen. The sample was seeded on 7% human blood agar and eosin methylene-blue agar plates and into fresh thioglycollate broth. The bacterial species were identified by colony morphology, Gram's stain, and biochemical reactions.

Immediately prior to kidney biopsy, blood urea nitrogen, nonprotein nitrogen, and creatinine were determined. Excretion of phenolsulfonphthalein (PSP) 15 minutes after the intravenous injection of 1 mg. was estimated by means of a Coleman Jr. spectrophotometer, and clearances of urea and endogenous creatinine were determined for a two-hour period with an average urine flow of more than 2 ml. per minute, that is, under conditions for maximal clearance of urea.

The measurements of effective renal plasma flow (ERPF), glomerular filtration (GFR), and tubular mass (Tm) were made by using inulin and *p*-aminohippuric acid (PAH), according to the methods of Goldring and Chasis.[13] The measurements were made in three consecutive 10-minute periods to establish each value. A calibrated infusion pump was used to maintain constant plasma levels of inulin and *p*-aminohippuric acid during the clearance periods. Plasma inulin levels at which clearance was measured varied among different persons between 20 and 40 mg. per 100 ml., and the *p*-aminohippuric acid level, between 1 and 2.5 mg. per 100 ml., with one exception (Patient J. G.), in which the levels were higher. For the measurement of tubular mass the plasma concentration of *p*-aminohippuric acid was between 35 and 55 mg. per 100 ml., with the same exception.

A Turkel needle with an internal diameter of 1.6 mm. was employed to obtain the kidney biopsy, using modifications of the technique described by Iversen and Brun,[9] Parrish and Howe,[12] and Kark and Muehrcke.[15] The patients were placed in a prone position with a sandbag under the hypogastrium. The needle was introduced below the 12th rib at the lateral margin of the sacrospinalis muscle, usually on the right side, and directed toward the location of the kidney, which was predetermined from an intravenous or retrograde pyelogram. After fixation of the tip of the needle in the renal substance, the stylet was replaced with a cutting needle, which was inserted approximately 2 cm. by rotation. The biopsy specimen was removed by gentle aspiration. The tissue that was obtained was divided under sterile conditions, and one fragment was placed immediately into 10% formalin. Later it was sectioned and stained with hematoxylin and eosin for microscopic examination. The second fragment was ground with sterile sand and cultured for bacteria on the same media used to culture the urine.

RESULTS AND REPORT OF CASES

A total of 20 patients were studied. One patient had acute pyelonephritis; 19 patients had persistent infection of the urinary tract

† References 10 and 11.

for many months or years, confirmed by repeated cultures of the urine. All these patients had failed to respond or they had had only a transient response to therapy with antibiotics on several occasions. Nearly all the patients had a recognized anatomical defect which contributed to the persistent infection. Nephrolithiasis was the commonest, and surgical removal of the stones had been accomplished in many of the patients several years before this study. Some patients had tortuous or dilated ureters or congenital abnormalities without gross obstruction of the ureteral system. One patient had polycystic disease of the kidneys.

The renal biopsies did not cause any serious complications. Microscopic and, rarely, gross hematuria was a constant consequence of a successful kidney biopsy. However, the hematuria always resolved within 24 hours after the biopsy. One patient described renal colic from the passage of some small blood clots, but otherwise there was no morbidity beyond the restrictions imposed upon the patients by their preceding disease. No evidence of exacerbation or extension of the infection was observed among these patients.

A biopsy of renal parenchyma suitable for pathologic interpretation was obtained from 13 patients. Normal kidney morphology was observed in four patients; chronic pyelonephritis was found four times, and the biopsies from the other five patients showed a "scarred" kidney, hydronephrosis, polycystic disease, necrotic tissue, and nephrosclerosis, respectively.

In correlating the bacteriologic, morphologic, and functional results it became apparent that the patients could be divided into three groups with nearly equal distribution of patients from whom adequate biopsy specimens were obtained. The case histories of representative patients in each group are given below:

GROUP I: INFECTED URINE, NORMAL KIDNEY STRUCTURE, AND NORMAL KIDNEY FUNCTION

CASE 1 (H. N., 33-14-66).—A 44-year-old white housewife was hospitalized because of a nine-year history of urinary tract disease beginning with recurrent bouts of right flank pain, fever, chills, and dysuria. These symptoms had occurred every three to four months and lasted five to six days each time. Sulfonamides usually were administered. During the preceding two years the acute episodes had subsided but she had constant mild right flank pain. In May, 1953, she received urethral dilatations and antibiotic therapy, without significant benefit. The bacteriologic studies and recorded treatment are given in Table 1.

TABLE 1.—*Results of Bacteriologic Cultures of Urine and Treatment Given Patient H. N., Case 1*

Date	Urine Culture	Therapy
1947	E. coli (both ureters)	Sulfonamides
1951	E. coli *	None
6/53	Micrococcus	Sulfonamides
10/53	Hemolytic Enterococcus & Micrococcus *	None
4/54	Hemolytic Enterococcus & E. coli *	Tetracycline

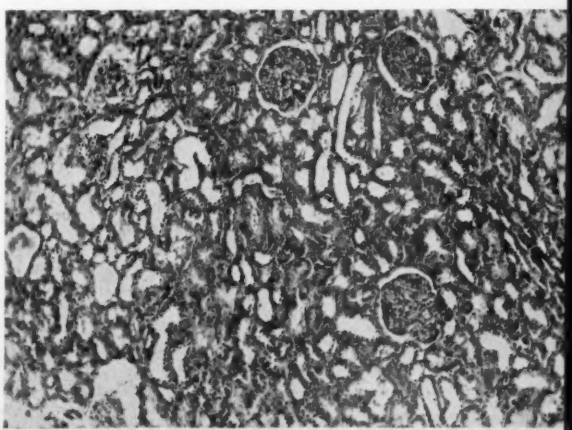
* Isolated from multiple urine specimens.

Physical examination was normal. The blood pressure was 98/70. Funduscopic and pelvic examinations were negative. Cystoscopic examination revealed mild chronic inflammation of the bladder. An intravenous pyelogram revealed a bifid right renal pelvis with blunting of the calyces and a normal left kidney.

The biopsy specimen from the right kidney (Fig. 1) was primarily of renal cortex and included many normal-appearing glomeruli. Both the proximal and distal tubules showed moderate distortion but no pathologic abnormalities. A urine culture taken at the time of biopsy revealed hemolytic enterococci and micrococci, but the culture of renal tissue showed no bacterial growth.

Comment.—This patient presented a nine-year history of chronic urinary tract disease

Fig. 1 (Case 1, H. N.).—Photomicrograph of a section of the kidney biopsy specimen, showing a normal kidney. The architecture is not altered, although the proximal convoluted tubules appear moderately distorted. The free margins of these tubular cells have a moth-eaten appearance due to the escape of cytoplasm into the lumen. The distal convoluted tubules are clear. There is no evidence of fibrosis or leucocytic infiltration.



and was found to have a congenital abnormality of the right kidney. There were repeated bouts of clinical acute pyelonephritis and chronic flank pain. From 1947 to the time of this study all urine cultures that were taken, except during drug therapy, revealed pathogenic micro-organisms. Kidney morphology, as revealed by biopsy, and also renal function studies were entirely normal, and bacteriologic culture of the kidney tissue yielded no growth. Chronic pyelonephritis, if it existed at all, must have been focal in nature, and it has not produced any measureable renal damage.

CASE 2 (M. Y., 35-84-98).—A 39-year-old white housewife developed a urinary tract infection, manifested by right groin pain, in the first trimester of her second pregnancy, in 1946. This pain recurred in attacks without other symptoms. After a normal termination of her pregnancy the pain persisted, and over the following three years various physicians diagnosed appendicitis, pelvic inflammatory disease, and cholecystitis. In 1949, during a third pregnancy, pelvic nephrolithiasis was found. A right nephrolithotomy in September, 1950, was followed by the disappearance of the symptoms until her fourth pregnancy, in 1951. Since that time the patient has had nearly constant urinary tract infection, as manifested by positive urine cultures, bacteriuria, and pyuria associated with intermittent attacks of dysuria and frequency of urination. The bacterial etiologies of the infection and the treatment are shown in Table 2.

Physical examination was normal except for a healed right flank scar. The blood pressure was 128/78. Funduscopic and pelvic examinations were normal. Cystoscopic examination was interpreted as showing chronic inflammation of the bladder.

Fig. 2 (Case 2, M. Y.).—Photomicrograph of a section of the kidney biopsy specimen, showing normal kidney. Many of the proximal convoluted tubular cells have irregular free margins due to rupture of their cells and release of cytoplasm. Many appear entirely normal. The single glomerulus to the right of the center field is compressed but shows no other unusual features. There is neither leucocytic infiltration nor increase in the interstitial tissue.

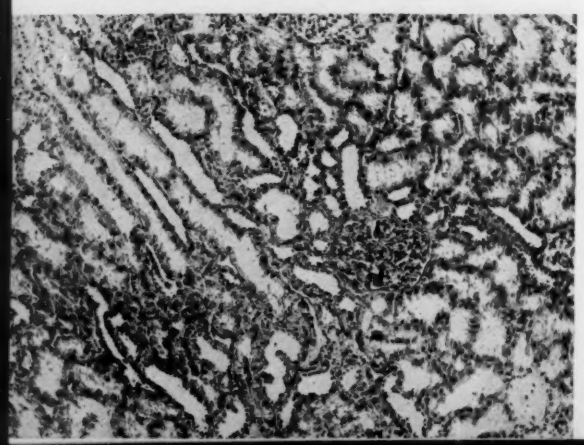


TABLE 2.—*Results of Bacteriologic Cultures of Urine and Treatment Given Patient M. Y., Case 2*

Date	Urine Culture	Therapy
1950	β-Hemolytic Streptococcus * †	Rt. nephrolithotomy; sulfonamides; penicillin, & streptomycin
1951	Coliform bacillus & E. freundi *	Sulfonamides
1952	A. aerogenes Proteus, & E. coli *	Closure of sinus tract plus chlortetracycline, sulfonamides, penicillin, & streptomycin
1953	Micrococcus *	None
1954	E. coli & Micrococcus	Tetracycline

* Isolated from multiple urine specimens.
† Serologic group not determined.

In 1950, a roentgenogram of the abdomen revealed stones in the pelvis of the right kidney. An intravenous pyelogram performed two years after nephrolithotomy showed the absence of stones but a deformed calyceal system of the right kidney and a normal pyelogram of the left kidney. Determinations of the serum calcium, phosphorus, and alkaline phosphatase levels were normal.

The biopsy specimen of the right kidney (Fig. 2) revealed both cortical and medullary structures characteristic of normal renal tissue, although the tubules exhibited evidence of some compression as a result of the biopsy technique. A urine culture taken at the time of biopsy revealed micrococci, whereas a culture of the renal tissue showed no growth.

Comment.—As in Case 1, this patient presented a nine-year history of chronic urinary tract disease. The first clinical symptoms were followed by nephrolithiasis, but four years of symptomatic bacteriuria and pyuria followed successful nephrolithotomy. However, the biopsy of the right kidney revealed no morphologic abnormalities; no bacteria were recovered from the renal tissue, and the kidney-function studies were normal. Thus, chronic pyelonephritis of a significant degree was not a concomitant of chronic bacteriuria and pyuria in this patient.

GROUP II: CHRONIC BACTERIURIA AND PYURIA WITH CHRONIC PYELONEPHRITIS AND DIMINISHED KIDNEY FUNCTION

CASE 3 (P. B., 32-27-00).—A 56-year-old white housewife was essentially well until 1946, when she developed frequent attacks of bilateral flank pain, hematuria, fever, chills, and cloudy urine. In 1946 and 1947 she passed several stones in the urine.

TABLE 3.—*Results of Bacteriologic Cultures of Urine and Treatment Given Patient P. B., Case 3*

Date	Urine Culture	Therapy
1946	γ Streptococcus & Staphylococcus albus	None
1947	γ Streptococcus, S. aureus & E. coli *	Rt. & Lt. nephrolithotomy, penicillin, & streptomycin
1948	E. coli & S. aureus *	Rt. ureter dilation, penicillin, & streptomycin
1949	S. aureus & E. coli	None
1951	S. aureus, E. Freundi, & Proteus	Sulfonamide, chlortetracycline
3/53	S. aureus, Proteus, & γ Streptococcus	Sulfonamides
10/53	S. aureus, paracolon, & Lactobacillus	None
4/54	S. aureus, Proteus, & γ Streptococcus	Penicillin, streptomycin, & tetracycline

* Isolated from multiple urine specimens.

Subsequently a bilateral nephrolithotomy was performed. In 1948 she had an exploratory operation of her left kidney, but no further repair or lithotomy was attempted. After the latter operation she had constant right flank pain, frequency of urination, nocturia, occasional hematuria, dysuria, and pyuria associated with bacteriuria, as demonstrated in Table 3.

On physical examination the blood pressure was 165/95. The fundi revealed minimal arteriosclerotic changes. The remainder of the physical examination was normal except for the operative scars. Cystoscopic examination showed chronic inflammation. Intravenous and retrograde pyelograms in 1947 revealed bilateral staghorn calculi before the operation and their absence after operation, but there were some narrowing of the right ureter and mild hydronephrosis on the right. The serum levels of calcium, phosphorus, and alkaline phosphatase were normal.

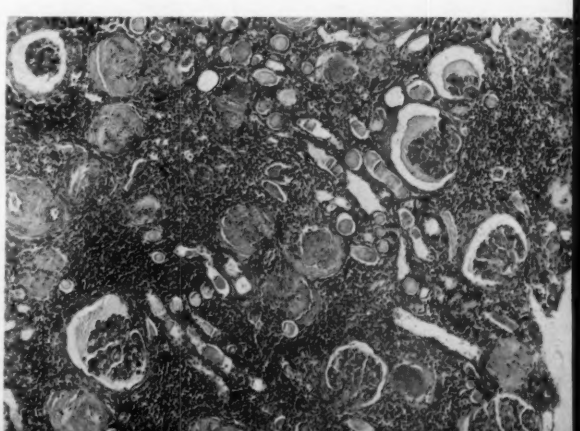
Microscopic examination of the kidney biopsy specimen (Fig. 3) revealed interstitial areas profusely filled with chronic inflammatory cells, and the majority of tubules were replaced by fibrosis and cellular infiltrate. The few remaining tubules were dilated and filled with hyaline-like material. The majority of the glomeruli were small and hyalinized. The arterioles were thick-walled and had small, compressed lumens. These findings were indicative of chronic pyelonephritis with vascular complications. The results of kidney-function tests were abnormal, and they will be presented later.

A urine culture taken at the time of biopsy revealed coagulase-positive Staphylococcus aureus (Micrococcus pyogenes var. aureus), paracolon, and Lactobacillus organisms. Culture of the renal parenchyma also produced a coagulase-positive S. aureus.

Comment.—This patient with chronic pyelonephritis had bacteriuria and pyuria over a nine-year period after the development of urinary calculi and a successful nephrolithotomy. The clinical history closely parallels that of Case 2, M. Y., who had only a benign infection insofar as renal damage was concerned. One apparent difference was the staphylococcic etiology of the infection; another was the age of the patient. At the time of renal biopsy, staphylococci were found in the renal parenchyma and urine simultaneously. The histologic changes, reduced kidney function, and hypertension represent classic severe chronic pyelonephritis, despite the successful surgery and treatment with several antibiotics.

CASE 4 (J. G., 40-07-76).—A 56-year-old white male tailor was essentially well until 1944, when he developed intermittent bouts of left flank pain with groin radiation. During the next five years he passed 17 stones in the urine, all accompanied by left flank pain. There was no history of chills or fever. He remained well from 1949 to 1951, at which time he developed painless hematuria. A right nephrolithotomy was performed, with a subsequent breakdown of the wound and the establishment of a draining sinus which persisted for 15 months. At no time did this tract seem to communicate with the renal pelvis. The patient remained clinically asymptomatic, although he continued to have cloudy

Fig. 3 (Case 3, P. B.).—Photomicrograph of a section of the kidney biopsy specimen, showing chronic pyelonephritis. This section shows extensive interstitial fibrosis and intense chronic inflammatory cell infiltration of the lymphocytic variety. Atrophy of the tubules is so advanced that their identity as to type can not be determined. Most of the lumens are filled with hyaline casts. The majority of the glomeruli are sclerosed, and hyalinized masses and periglomerular fibrosis are present. In the less altered glomeruli, early hyalinization is apparent. There are no synechiae between the glomerular and capsular epitheliums. The arterioles, as seen at the extreme left, have undergone intimal hyalinization. The peritubular blood vessels can not be well visualized.



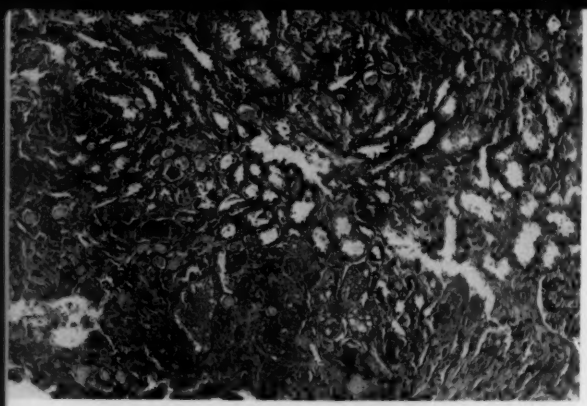


Fig. 4 (Case 4, J. G.).—Photomicrograph of section of the kidney biopsy specimen, showing chronic pyelonephritis. The microscopic field shows the corticomedullary junction. Fibrous tissue is increased, as seen at the left, obliterating and replacing the atrophic tubules. Some of the latter contain small casts. A few small aggregates of chronic inflammatory cells are dispersed throughout. The lumens of proximal convoluted tubules in the lower center are filled with an amorphous refractile substance. The tubular cells here show pronounced granularity and vacuolization. In the lower right a portion of a normal-appearing glomerulus is seen, with adjacent fibrosis.

urine. The bacteria isolated from the urine and the treatment administered are noted in Table 4.

Physical examination was normal. The blood pressure was 130/72. Funduscopic examination was negative. Serum, calcium, phosphorus, and phosphatase levels were normal.

Microscopic sections of the kidney biopsy specimen (Fig. 4) revealed many dilated tubules containing acidophilic hyalin masses. The interstitial tissue was irregularly fibrous, while the glomeruli appeared normal except for a rare hyalinized one. These findings were believed to indicate chronic pyelonephritis.

Urine cultures taken at the time of biopsy revealed Pseudomonas aeruginosa and Enterococcus. Culture of the renal parenchyma showed no bacterial growth.

In January, 1954, a plastic repair of an obstruction at the right ureteropelvic junction was attempted, but because of scar tissue this procedure was unsuccessful, and a nephrostomy tube was left in place. Because of this it was possible to perform

TABLE 4.—*Results of Bacteriologic Cultures of Urine and Treatment Given Patient J. G., Case 4*

Date	Urine Culture	Therapy
4/53	Pseudomonas & Enterococcus *	None
10/53	Pseudomonas & Enterococcus *	Sulfonamide
11/53	Pseudomonas & Enterococcus *	Chlortetracycline
1/54	Pseudomonas & Enterococcus *	Penicillin & streptomycin
4/54	Pseudomonas *	Penicillin & streptomycin

* Isolated from multiple urine specimens.

TABLE 5.—*Results of Bacteriologic Cultures of Urine and Treatment Given Patient A. C., Case 5*

Date	Urine Culture	Therapy
1949	A. aerogenes *	None
1950	A. aerogenes *	Rt. & Lt. nephrolithotomy; penicillin & streptomycin
1951	Pseudomonas *	Rt. nephrolithotomy
2/53	Pseudomonas *	None
11/53	Pseudomonas, Proteus, & γ Streptococcus *	Tetracycline

* Isolated from multiple urine specimens.

separate kidney-function studies of the right (via the nephrostomy tube) and the left (via the bladder catheter) kidney. X-ray studies established the completeness of the right ureteral obstruction at this time.

Comment.—The clinical history of this patient over the past 10 years has been predominated by renal lithiasis, while the associated bacteriuria and pyuria produced very few symptoms. However, biopsy of the right kidney revealed advanced chronic pyelonephritis. The patient afforded the opportunity to measure the function of the kidneys separately, and these studies indicated the preponderant functional severity of the lesion on the right side. In spite of this, the blood pressure was normal. Bacteriologic culture of the renal tissue was negative, although the urine obtained from both the nephrostomy and the bladder was infected.

CASE 5 (A. C., 30-85-23).—A 33-year-old Negro housewife noted the onset of left flank and groin pain in 1946, at the age of 26. In 1949, nephrolithiasis, rheumatoid arthritis, cutaneous nodules, atrophy of the right parotid gland, pulmonary fibrosis, anemia, and hepatosplenomegaly resulted in a clinical diagnosis of sarcoidosis. After her discharge from the hospital, flank pain and dysuria waxed and waned and the patient required hospitalization on several occasions. On one occasion she passed a kidney stone associated with hematuria and right flank and groin pain. Later in 1949, a bilateral nephrolithotomy was performed. She continued to have cloudy urine and occasional dysuria, and in 1951 a staghorn calculus was removed from the right kidney. Since that time the patient has had persistently infected urine, with recurrent attacks of bilateral flank and groin pain, dysuria, frequency of urination, and nocturia, without the recurrence of renal stones. The bacterial cultures and treatment are shown in Table 5.

Physical examination revealed a blood pressure of 122/82. Funduscopic examination was normal. The voice was harsh; there was a chronic nonproductive cough; the nasal and buccal mucosa were atrophic, and there was bilateral keratitis. The liver and spleen were enlarged. Pelvic examination was normal. Cystoscopy revealed chronic inflammatory changes in the bladder. Serum calcium and phosphorus were normal.

The kidney biopsy specimen (Fig. 5) showed hypertrophy of the proximal convoluted tubules. Many of the distal tubules were plugged with acidophilic hyalin substance. A few contained basophilic calcareous debris. In some regions the interstitial connective tissue was increased, obliterating and compressing the nephron elements. The findings were compatible with a diagnosis of chronic pyelonephritis. The kidney-function tests were abnormal and will be discussed later. A urine culture taken at the time of biopsy revealed P. aeruginosa, Proteus species, and γ Streptococcus. Culture of the renal parenchyma produced no bacterial growth.

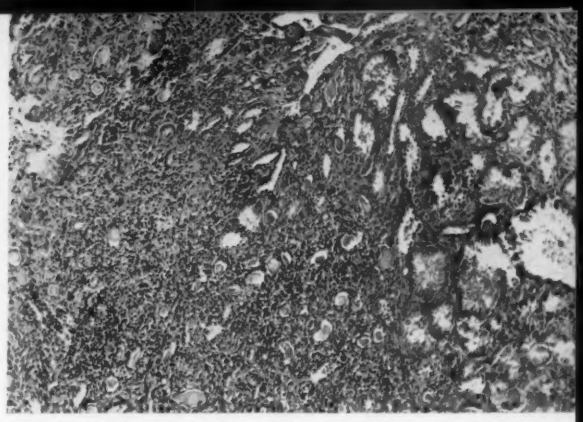


Fig. 5 (Case 5, A. C.).—Photomicrograph of a section of the kidney biopsy specimen, showing chronic pyelonephritis. The intense fibrosis and infiltration with inflammatory cells involving primarily the outer medullary zone are notable to the left. The tubules here are atrophic, compressed, or obliterated, and many contain hyaline casts. In the juxtamedullary cortex to the right dilated and hypertrophied tubules, principally convoluted, are seen. No glomeruli are included, but in other fields normal and occasional hyalinized glomeruli were seen. The capillaries are difficult to perceive. Arterioles as visualized elsewhere showed endothelial hyperplasia and intimal hyalinization.

Comment.—This young adult had a nine-year history of renal disease. The initial symptoms may have been related to an unrecognized renal stone, but whether the stone was complicated by infection or vice versa, both conditions existed when she entered the hospital, and bacteriuria and pyuria continued after nephrolithotomy. A renal stone recurred, and urinary tract infection has continued three years after the second successful surgical removal of a calculus. The function of the kidneys was markedly impaired. Bacteriologic culture of the renal biopsy tissue was negative. Hypertension was not present. Hypercalcuria was suggested by the biopsy, despite normal serum calcium, phosphorus, and phosphatase. Regardless of the cause and effect relationship of the infection and the stones, the net result has been a severe chronic pyelonephritis.

Group III: Acute or Intermittent Bacteriuria and Pyuria with a Structural Abnormality of the Kidney and Variable Kidney Function

Case 6 (M. U., 35-95-77).—A 56-year-old white housewife had scarlet fever at the age of 8 but remained essentially well until 1945, when she developed frequent bouts of left flank pain with groin radiation, fever, chills, frequency of urination, and cloudy urine. In 1950 a left nephrolithotomy was performed. After this procedure she remained well until January, 1953, when she again developed left flank pain, fever, dysuria, and cloudy urine, without apparent recurrence of a stone. Treatment with sulfonamides and chlortetracycline was associated with the disappearance of the acute symptoms, but there remained a persistent dull left flank pain, occasional dysuria, and some frequency of urination. Bacteriuria was common. The results of bacteriologic cultures of the urine and some of the treatment given are shown in Table 6.

Physical examination revealed the blood pressure to be 155/85. The fundi showed a minimal decrease in the artery-vein ratio and some spasm of the peripheral arterioles. There was a soft apical systolic murmur. The abdomen was tender on deep palpation in the right and left upper quadrants. No masses were palpable. Intravenous and retrograde pyelograms prior to 1950 revealed a left kidney stone with mild hydronephrosis. Recent pyelograms were not abnormal, and cystoscopy showed only mild inflammation of the bladder. The serum levels of calcium and phosphorus were normal.

Microscopic examination of the kidney biopsy specimen (Fig. 6) revealed slightly dilated tubules

Table 6.—*Results of Bacteriologic Cultures of Urine and Treatment Given Patient M. A., Case 6*

Date	Urine Culture	Therapy
1949	E. coli *	Sulfonamides
1950	E. coli & Proteus *	Lt. nephrolithotomy; penicillin, streptomycin, & sulfonamides
7/53	E. coli	Sulfonamides & chlortetracycline
10/53	E. coli	None
5/54	E. coli	Tetracycline

* Isolated from multiple urine specimens.

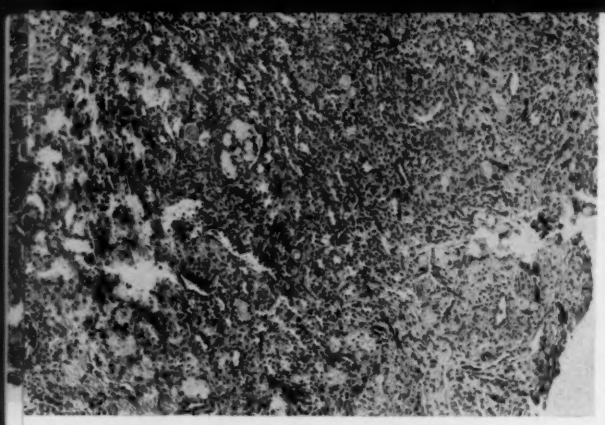


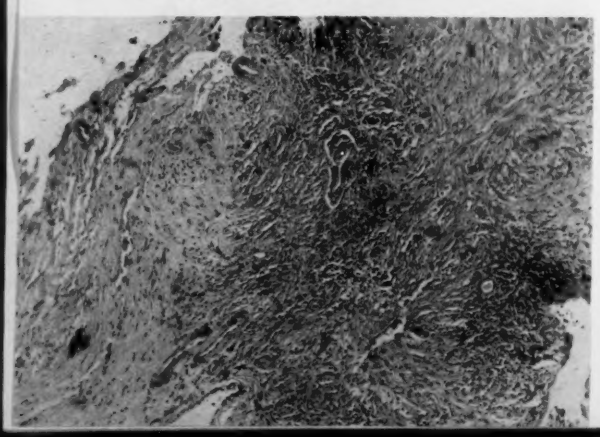
Fig. 6 (Case 6, M. U.).—Photomicrograph of a section of the kidney biopsy specimen, showing a scarred kidney consistent with healed pyelonephritis. The section includes the corticomedullary junction, and, although there is some distortion, the right half of the section (medullary) shows extensive overgrowth of poorly vascularized fibrous interstitial tissue, with tubular compression and atrophy. There is only a modest spotty infiltration with chronic inflammatory cells. Many of the convoluted tubules, as seen at the left, contain amorphous debris (liberated tubular cytoplasm). Tubular casts are seen in many areas. A small hyalinized glomerular tuft, barely identifiable as such, is found just to the left of the central field. The majority of the vascular channels are not well discerned because of the fibrosis.

containing homogenous pink fluid. Patchy areas of fibrosis were scattered about the tubules. The glomerular tufts did not appear abnormal. The findings were indicative of a scarred kidney consistent with healed chronic pyelonephritis.

Urine culture taken at the time of biopsy revealed Escherichia coli. Cultures of the kidney tissue were sterile.

Comment.—The patient's history represents an episode of acute and possibly chronic pyelonephritis associated with a renal stone. Treatment that included nephrolithotomy was apparently successful until the recurrence of infection three years later. Biopsy of the kidney revealed fibrous scarring, possibly healed chronic pyelonephritis. Kidney function was normal except for a reduction in the tubular mass. No bacteria were recovered from the kidney, and there was no hypertension.

Fig. 7 (Case 7, I. B.).—Photomicrograph of a section of the kidney biopsy specimen, interpreted as consistent with polycystic kidney disease. Dispersed in the dense fibrous stroma are atrophic tubular structures identifiable by their residual epithelial cells. At the right, surrounded by an intense chronic inflammatory cell reaction, is a small but prominent tubule containing a cast. In the center field, above a poorly defined zone of acute and chronic inflammation, are collapsed tubular remnants. The vascular channels are few. No glomeruli are included.



Case 7 (I. B., 39-43-48).—A 55-year-old Negro housewife first noted a mass in her right side 30 years ago. She had no symptoms related to the mass until five years prior to admission, when she developed nocturia. In September, 1952, she noted low back pain, hematuria, and dysuria. A diagnosis of bilateral polycystic disease of the kidney was made. In November, 1953, she developed dysuria, fever, shaking chills, and cloudy urine. The symptoms persisted for two weeks despite antibiotic therapy. Since that time she has had five or six similar recurrences. Two sisters previously had died of polycystic kidney disease. Bacteriologic cultures of the urine are shown in Table 7.

Physical examination revealed a blood pressure of 160/100. The fundi were normal. Positive findings were limited to the abdomen. The right kidney was large, firm, and nontender. It moved with respiration and was palpable in the right flank. The left kidney also was palpable. Retrograde pyelography confirmed polycystic disease.

Table 7.—*Results of Bacteriologic Cultures of Urine and Treatment Given Patient I. B., Case 7*

Date	Urine Culture	Therapy
9/52	E. coli	Sulfonamides
10/52	E. coli *	None
10/53	E. coli *	Chlortetracycline
1/54	E. coli *	None
4/54	E. coli	Tetracycline

* Isolated from multiple urine specimens.

The microscopic sections of the kidney biopsy specimen (Fig. 7) showed dense cellular collagenous tissue. In several poorly circumscribed parts of the stroma were regions of intense, acute, and chronic inflammation. Fragmented and degenerating collagen fibers were present as well as lysed polymorphonuclear cells. The adjacent areas were moderately edematous. A few margins of the tissue were edged by a single layer of cells. A scant number of renal tubules were present. The fibrosed renal tissue was believed to be compatible with the clinical diagnosis of polycystic kidney. Renal function tests showed impairment and will be discussed. Urine cultures and cultures of the cyst fluid and of renal tissue, taken at the time of biopsy, were all infected with E. coli.

Comment.—This patient with congenital cystic disease of the kidneys was free of urinary tract symptoms until age 50. In the five years since that time she has had persistently infected urine, with recurrent attacks of clinical acute pyelonephritis. The kidney biopsy showed areas of acute and chronic inflammation. She now has hypertension and renal insufficiency. The cyst fluid, the fibrous renal tissue, and the urine were infected with E. coli. The role of the infection in accelerating renal failure cannot be ascertained with certainty, but it appears to have been important.

TABLE 8.—*Results of Urinalysis in Patients with Chronic Urinary Tract Infection Classified by Kidney Morphology and Function*

	Group I: Infected Urine, Normal Structure, and Normal Function		Group II: Infected Urine, Chronic Pyelonephritis, and Decreased Function			Group III: Infected Urine, Abnormal Structure, and Disproportionate Function	
Urine	H. N. Case 1	M. Y. Case 2	P. B. Case 3	J. G. Case 4	A. C. Case 5	M. U. Case 6	I. B. Case 7
Appearance	Cloudy	Clear	Cloudy	Cloudy	Cloudy	Clear	Cloudy
Reaction, pH	5.5	5.5	5.5	5.5	5.5	6.0	5.5
Specific gravity	1.016	1.018	1.014	1.010	1.008	1.010	1.012
Albumin	0	0 to trace	+	0	+	0	++
Epithelial cells	Occas.	Rare	0	0	Occas.	Rare	Occas.
Leucocytes	2-10/HPF	6-18/HPF	20-30/HPF	9-12/HPF	Many/HPF	2-8/HPF	10-18/HPF
Erythrocytes	Occas.	2-5/HPF	2-3/HPF	Rare	4-20/HPF	1-2/HPF	1-2/HPF
Hyaline casts	0	0	0	0	Rare	0	0
Granular casts	0	0	1-2/HPF	0	1-5/HPF	0	Rare
RBC casts	0	0	0	0	0	0	0
WBC casts	0	0	Occas.	0	1-3	0	Rare
Supravital stain *	Negative	Negative	Negative	Negative	Positive	Negative	Negative
Gram stain †	Positive	Negative	Negative	Positive	Positive	Positive	Positive
Urine culture	E. coli, enterococci	Micrococci	Staphylococcus, paracolon	Pseudomonas, enterococci	Pseudomonas, Proteus, Paracolon, Streptococcus	E. coli	E. coli
Kidney culture	No growth	No growth	S. aureus	No growth	No growth	No growth	E. coli
Biopsy	Normal	Normal	Chronic pyelonephritis	Chronic pyelonephritis	Chronic pyelonephritis	Scarred kidney (healed pyelonephritis)	Polycystic kidney

* The wet sediment from 15 ml. of dilute urine resuspended in 0.5 ml. was stained with an alcoholic solution of gentian violet and safranine, and a smear was examined microscopically. The terms positive and negative refer to the presence or absence of large pale blue leucocytes with vacuolization of the cytoplasm and movement of the cytoplasmic inclusions.

† A heat-fixed smear of the sediment from 15 ml. of urine stained by Gram's method. The terms negative and positive refer to the presence or absence of definite bacteria on the smear.

URINALYSIS

The results of urinalyses of freshly obtained first morning specimens, examined by the usual clinical methods, are shown in Table 8. All these examinations were performed by one of us (G. P. K.), and the results are believed to be characteristic of what can be expected from a carefully performed routine urinalysis. Cloudy urine was common among the patients who were found to have pyelonephritis. A moderate number of leucocytes were present in the sediment, and occasionally there were white blood cell casts. However, by these methods the number of leucocytes in the urine of persons with and without morphologic and functional evidence of pyelonephritis, but with a chronic urinary tract infection, were not different. Erythrocytes and hyaline and blood casts in the sediment were rare. Albuminuria was indicative of renal involvement when it was present, but it was not detected in all the patients with pyelonephritis, and of course it was not specific for pyelonephritis. Albuminuria was never massive; it was usually slight, and, roughly, it was directly related to the degree of functional kidney impairment.

Microscopic observation of the supra-vital-stained sediment was performed to identify large pale-staining leucocytes with vacuoliza-

tion of the cytoplasm and vigorous movement of the cytoplasmic granules—"pyelonephritis cells" as described by Sternheimer and Malbin.[14] Such cells were found infrequently, but when they were seen the patients had pyelonephritis upon biopsy also. Bacteria were not always found in the Gram-stained smear of the sediment.

Bacteriologic cultures of the urine were uniformly positive, and several different species of micro-organisms were isolated. Bacteriologic cultures of a fragment of renal tissue obtained from the biopsy, in contrast to the urine obtained nearly simultaneously, were negative with only two exceptions. In these two instances, the organism obtained from the kidney was the same species as the one recovered from the urine.

TABLE 9.—*Tests of Kidney Function Used for Clinic Patients*

Test *	Approximately Normal	Group I: Infected Urine, Normal Structure & Function		Group II: Infected Urine, Chronic Pyelonephritis, & Decreased Function			Group III: Infected Urine, Abnormal Structure, & Disproportionate Function	
		H. N. Case 1	M. Y. Case 2	P. B. Case 3	J. G. Case 4	A. C. Case 5	M. U. Case 6	I. B. Case 7
BUN	12	9.7	12	16.4	20	36	11.2	43.7
NPN	35	24	34	42	57	74	34	162
Creatinine	1.0	0.9	0.8	1.3	2.1	2.1	0.8	4.6
12-hr. concentration	1.026	1.026	1.028	1.014	1.010	1.010	1.016	1.012
PSP (15 min., I. V.)	>25	45	45	17	18	10	36	Too little to measure
Urea (max.)	70	65	50	38	18	20	64	6
Creatinine	115	100	118	88	32	57	106	11

* The results shown were obtained from the first test performed carefully with the patient in a fasted and resting state. The values are corrected to 1.73 sq. meters of surface area.

TABLE 10.—*Quantitative Measurement of Kidney Function*

Measurement *	Approximately Normal	Group I: Infected Urine, Normal Structure & Function		Group II: Infected Urine, Chronic Pyelonephritis, & Decreased Function				Group III: Infected Urine, Abnormal Structure, & Disproportionate Function	
					J. G. Case 4				
		H. N. Case 1	M. Y. Case 2	P. B. Case 3	Rt.	Lt.	A. C. Case 5	M. U. Case 6	I. B. Case 7
ERPF (C_{PAH}) ml./min.	600	585	565	272	6	259	150	658	14.1
GFR (C_{IN}) ml./min.	120	113	105	61	1	62	27.6	125	4
FF $\frac{(C_{IN})}{(C_{PAH})}$ %	20	19.4	18.6	22.4	17	24	18.4	19	28
T_{mPAH}, mg./min.	75	76.2	81.9	48	0.3	39.3	17	45	1.7
C_{PAH}/T_{mPAH}	8.0	7.7	6.9	5.7	20	6.5	8.3	14.8	8.3
C_{IN}/T_{mPAH}	1.6	1.5	1.3	1.2	3.3	1.6	1.6	2.8	2.4

* All values are corrected to 1.73 sq. meters of surface area.

KIDNEY FUNCTION

The results of tests that are commonly used for evaluation of kidney function in clinic patients are shown for the cases presented in Table 9. All the tests that were employed served rather well to separate those patients who subsequently showed chronic pyelonephritis in the kidney biopsy from the group who had a normal kidney biopsy. The blood concentration of urea or nonprotein nitrogen was elevated above normal in all the patients whose kidney biopsy revealed chronic pyelonephritis, as well as in the patient with infected polycystic kidney disease, but the BUN and NPN were normal in all the other patients, including one with an infected hydronephrosis. Simply withholding fluids for 12 to 14 hours and determining the specific gravity of the morning urine specimen screened the patients into those who did and those who did not show a diminished tubular mass, when the latter was measured by excretion of *p*-aminohippuric acid. An intravenous phenolsulfonphthalein test contributed little additional information, and

sometimes it was difficult to correlate quantitatively with other tests. The clearance of urea and endogenous creatinine from the blood, with a urine flow suitable for maximal clearance in the case of urea, enabled only a rough quantitative estimate of the decreased glomerular filtration when it was abnormal. In the presence of severe renal disease the creatinine clearance was falsely high.

The results from quantitative measurement of kidney function using inulin and *p*-aminohippuric acid are presented in Table 10, with observation of separate function of the right and left kidneys in Patient J. G. (Case 4). It is apparent from the Table that the effective renal plasma flow was markedly reduced in the patients with chronic pyelonephritis. The glomerular filtration rate also was decreased in these cases proportionally to the decreased plasma flow, as is indicated by the relatively normal filtration fraction. This suggests the absence of any specific functional glomerular lesion.

The renal tubular mass also was found to be reduced in all the patients who had a significant abnormality in the morphology of the kidney as shown by biopsy. The decrease in tubular mass among the patients with chronic pyelonephritis also was proportional to the decrease in renal plasma flow, with the exception of the right kidney in Patient J. G., in which instance both functions were negligible. Furthermore, among the patients with chronic pyelonephritis the tubular mass was normally proportional to the glomerular filtration rate, indicating insignificant selective tubular damage or, alternatively, functional glomerular sparing. At constant high plasma concentrations of *p*-aminohippuric acid these patients with chronic pyelonephritis did not show an increase in tubular mass during consecutive periods. This was observed by Raaschou [16] among some patients with severe pyelonephritis and interpreted as evidence for functional tubules isolated by poorly vascular fibrous tissue.

In the two patients with a morphologic abnormality of the renal parenchyma classified in Group III, the reduction in tubular mass did appear to exceed the impairment of renal plasma flow and glomerular filtration. In Patient M. U. (Case 6), whose biopsy showed a scarred kidney (possibly healed pyelonephritis), the maximum secretion of *p*-aminohippuric acid was only approximately 60% of normal, although the effective renal plasma flow and glomerular filtration rate were high-normal values. The selective tubular insufficiency is indicated by the abnormally high ratios of C_{PAH}/Tm_{PAH} and C_{In}/Tm_{PAH}. In contrast to the results in the patients with active chronic pyelonephritis, the tubular mass approximately doubled in function between the first and second clearance periods with a constant high plasma concentration of *p*-aminohippuric acid, suggesting that the perfusion of marginal tubules was attained.

In the patient with polycystic disease, the tubular mass was extremely small and there was an increased filtration fraction and C_{In}/Tm_{PAH} ratio, indicating the relative persistence of glomerular function in polycytic disease, as has been observed previously.[17] Whether the kidney infection increased the tubular deficit beyond that due to the polycystic disease alone is not known. Since the C_{PAH}/Tm_{PAH} ratio was nearly normal, without any progressive increase in the tubular mass during three consecutive periods of measurement, one can assume that an insignificant number of marginal tubules were perfused by diffusion through cyst fluid or poorly vascularized tissue.

GENERAL COMMENT

The clinical histories of this group of patients with persistent urinary tract infection are very similar. All the patients had infected urine over a period of several months, and usually over a period of several years, commonly associated with an anatomic anomaly or nephrolithiasis. It seemed to us at the outset that all of them would show some stage of chronic pyelonephritis, and it was surprising to find one-third of the patients with normal kidney morphology and function. There is very little in the clinical histories of Cases 2 and 3, for instance, to account for the great differences found in the biopsy

specimens (Figs. 2 and 3) and kidney function. Also, micro-organisms were isolated from the renal parenchyma of the latter patient and not from the former. If focal pyelonephritis away from the biopsy site explains the findings in patients with normal biopsy specimens, it was without a detectable influence upon kidney function and therefore was of minor importance at the time of the studies. Similarly, Brun and co-workers [11] performed kidney biopsies upon eight patients with infected urine and a clinical diagnosis of pyelonephritis, and the biopsy supported the diagnosis in only one of the eight patients.

These experiences might again raise speculation as to whether lower urinary tract infection or even pyelitis or focal pyelonephritis might persist for years as localized infection without producing measurable kidney damage. Also, one might consider whether the relatively unknown capacity of different strains and species of micro-organisms to produce pyelonephritis is important, as well as factors such as the presence of protective (colloid) and bacteria-stimulating (carbohydrate) substances in the urine. The age of the patient, as well as the duration of the infection, also might significantly influence the nature of the lesion; another unknown consideration is the effect of hydrostatic pressure caused by obstructive uropathy in some patients. These are factors that need further elucidation for an understanding of the pathogenesis of pyelonephritis and for its differentiation from benign urinary tract infections.

Renal lithiasis was unusually common among the patients selected for these studies. In some instances the clinical history indicated that the renal stones anteceded the development of urinary infection. One may wonder what proportion of the renal impairment was caused by the local and metabolic conditions that led to the formation of the stones. The data are not sufficient to give a categorical answer, but they suggest a minor role. Infections usually appeared to be the primary cause of the pathologic renal lesion, even though the chronic infection was secondary to anatomic uropathy. The patient who was believed to have sarcoid is of interest in view of the recent observation of abnormally high calcium excretion by some patients with that disease.[18] She had bilateral recurrence of urinary calculi, and calcareous debris was observed within the tubules in the biopsy specimen.

Urinalysis and microscopic examination of the urine sediment were helpful but inconclusive in distinguishing patients with chronic pyelonephritis from others with infected urine. The degree of bacteriuria and pyuria, as has been pointed out by previous investigators,[14] is not an index of the severity or extent of the urinary infection. On the other hand, the ability to concentrate urine to a specific gravity of 1.026 in the absence of albuminuria and a normal urea clearance test are good evidences for the lack of significant kidney damage. Longcope [8] called attention to the tendency for patients with pyelonephritis to secrete a persistently hypotonic urine for many years. The formation of a concentrated urine has generally been considered a tubular function. However, the work of Baldwin and his associates [19] indicates that the ability to form a hypertonic urine deteriorates in proportion to the glomerular filtration rate, thus relating concentration ability to the loss of functioning nephrons rather than to specific tubular dysfunction.

The low incidence of positive bacteriologic cultures from the renal parenchyma among patients with infected urine may indicate bacterial strains of low virulence, individual factors leading to resistance of the kidney to infection, or focal infection, not included in the biopsy. When micro-organisms were isolated from the renal tissue they were apparently from the same strain as was found in the urine, and severe alteration of the renal morphology was evident in the biopsy.

The performance of renal biopsy is not a technically difficult procedure, and with adequate precautions little morbidity was observed. However, until further experience and the contributions of the procedure are established we feel that its use should be restricted.

An early and reasonable criticism of the kidney biopsy technique was whether or not the tissue that was obtained would be adequate or reliably representative for interpretation. Especially in a disease such as pyelonephritis, which may produce only focal areas of inflammation, this criticism must be accepted. In the present experience, however, there was no instance in which a normal biopsy specimen was obtained from a patient with appreciably abnormal function, and, likewise, a morphologic abnormality in the renal biopsy was associated with definite impairment of one or another of the functional modalities that were studied. Thus, the correlation between the kidney morphology, as seen in the biopsy, and kidney function was relatively good, although the degree and type of functional impairment of the kidney could not be judged reliably from the microscopic examination of the biopsy specimen. This is in agreement with the studies of Parrish and his associates [20] in other types of renal disease. Observations have been made at the autopsy table by comparing single biopsy specimens with multiple blocks of tissue taken from the same kidney, and they corroborate the general reliability of the biopsy in reflecting the diffuse morphology of the organ when five or more glomeruli are examined.‡

The morphologic alterations observed in chronic pyelonephritis have several components, any one of which might dominate the microscopic picture. A description of the changes was given in detail by Weiss and Parker,[4] who also concluded that the structural characteristics of pyelonephritis were essentially the same whether the infection was hematogenous, ascending, or lymphogenous in origin. An increase in the interstitial tissue, with a chronic inflammatory reaction and sometimes fibrous tissue, was prominent in the biopsies interpreted here as showing pyelonephritis (Figs. 3, 4, and 5). Also, the occurrence of hyaline casts in many of the tubules was common, and this was usually associated with flat, apparently atrophic tubular epithelium, although adjacent tubules sometimes appeared quite normal. Peritubular and periglomerular fibrosis were sometimes prominent. Random hyalinized glomeruli were common (Fig. 3); otherwise, morphologic changes in the blood vessels were not great.

The functional impairment associated with the histologic picture of active chronic pyelonephritis was principally a decrease in the effective renal plasma flow. The glomerular filtration and tubular mass were not selectively impaired but rather sometimes showed a tendency toward compensatory function relatively greater than that expected for the observed plasma flow. Since the calculation of effective renal plasma flow is based on the quantitative excretion of *p*-aminohippuric acid, when the blood concentration of this substance is low, the observed values may be significantly erroneous when the functioning tubular mass does not extract more than 90% of the load. The renal arteriovenous *p*-aminohippuric acid extraction ratios were not measured in these patients, but it seems likely from the observations of Cargill [21] and of Bradley and his co-workers [22] that the extraction ratios might have been reduced to the range of 0.75 to 0.85. When this correction was applied, however, diminished renal plasma flow still appeared to be the outstanding deficit in the patients with pyelonephritis, but, since the number of patients studied completely is small, generalizations must be reserved.

These data on kidney function were somewhat unexpected in view of the histological findings of interstitial and tubular morphologic lesions with some relative sparing or late involvement of the glomeruli and other vessels. The findings are at variance with the early report of Raaschou,[23] who suggested that the functional lesion of pyelonephritis also selectively affected the tubules, causing a glomerulotubular disproportion, which he observed by comparison of the urea clearance and the ability of the kidneys to concentrate the urine. Additional later studies by the same author,[16] using inulin and iodopyracet (Diodrast) clearance have both supported

‡ Pirani, C. L., and Dallenbach, F. D.: Unpublished data.

and modified his earlier interpretations. Bradley and his associates [22] have noted the observations of Raaschou and have presented data on four additional patients with clinical chronic pyelonephritis. The most uniform abnormality in the kidney function of these patients was a decrease in the *p*-aminohippuric acid extraction ratio. In agreement with the results reported here, the estimated renal plasma flow was diminished in three of the four patients, but, in contrast to most other reports, the filtration fraction also was decreased in three of them. In two patients the tubular mass was diminished more significantly than the decrease in renal blood flow, but in one there was a similar reduction in the glomerular filtration rate. In the case of pyelonephritis studied with biopsy and clearance techniques reported by Brun and his colleagues [11] there was an equal reduction in glomerular filtration and tubular mass, but the renal blood flow was not given.

Among five patients with chronic pyelonephritis and hypertension studied by Corcoran and his associates,[24] the pattern of impaired renal function was nearly identical with that observed in their group of patients with established essential hypertension and indicated no selective tubular damage.

The data obtained allow the speculation that the selective tubular impairment sometimes observed in patients with chronic pyelonephritis (Case 6) might be more characteristic of the healed or fibrotic stage than it is of the chronic inflammatory stage, in which reduction of blood flow with equal impairment of glomerular and tubular function is more characteristic.

The severe decrease in effective perfusion of the kidneys in pyelonephritis logically relates the disease to its role in the production of hypertension § in a manner similar to that of the experimental ischemic kidney of Goldblatt.[26] There are a few well-documented cases in which hypertension was cured by the removal of a diseased kidney in patients with unilateral chronic pyelonephritis.[7] Two of the patients studied here in whom the kidney disease seems to have been primary had hypertension. Another patient was found to have a severely ischemic kidney on one side (Case 4) without hypertension.

A recent survey of the incidence of pyelonephritis during the antibiotic era [6] revealed a significant decrease in the frequency of its occurrence in the autopsies within recent years. It is hoped that the application of techniques presently available for investigation of the kidneys might lead to further clarification of the pathogenesis and consequently a reduction in the incidence of pyelonephritis and its complications.

SUMMARY AND CONCLUSIONS

Twenty patients with persistent or frequently recurrent urinary tract infections have been carefully evaluated by clinical and bacteriologic methods, and some of them, by means of kidney biopsy and renal clearance techniques with respect to the presence of chronic pyelonephritis. Nearly all the patients had a known anatomic abnormality that contributed to the urinary infection. The clinical picture was variable; most of the patients were free from constitutional symptoms, but they suffered from dysuria, frequency of urination, and backache. One patient had acute pyelonephritis. Representative case histories are presented.

Kidney biopsy was successfully performed on 13 of the patients, and the tissue that was obtained was used for histologic and bacteriologic study. The microscopic appearance of the kidney biopsies was sometimes normal, sometimes consistent with pyelonephritis. These changes are illustrated by photomicrographs. Bacteriologic cultures of the renal parenchyma were negative in all but two instances. No complications were encountered.

Correlation of kidney morphology and kidney function was relatively good and enabled the classification of the patients with infected urine into three categories, as follows: (1) those with normal kidney morphology and function, (2) those with pathologic changes characteristic of active chronic pyelonephritis associated with diminished renal function, and (3) those with abnormal renal structure

§ References 4 and 25.

other than, or in addition to, pyelonephritis, sometimes associated with disproportionate glomerulotubular function.

The principal functional defect observed among the patients with chronic pyelonephritis was a diminished effective renal plasma flow. The glomerular filtration rate and the tubular mass were proportionately and equally reduced. In a patient with a scarred kidney, probably a healed pyelonephritis, selective tubular impairment was observed.

Dr. Joseph H. Kiefer and his associates in the division of urological surgery assisted in this study.

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Milk-Alkali Syndrome

Review of Eight Cases

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Burnett and associates,[1] in 1949, reported six cases presenting the following features: (1) hypercalcemia without hypercalciuria or hypophosphatemia, (2) calcinosis manifested especially by ocular lesions resembling band keratitis, and (3) renal insufficiency with azotemia, following the prolonged intake of milk and absorbable alkalis, usually for treatment of active peptic ulcer. This clinical entity has become known as the "milk-alkali syndrome." Since Burnett's initial description there have been sporadic reports of cases,* some of which have stressed complications such as metastatic calcification, nephrocalcinosis, and renal calculi. The early signs and symptoms produced by this syndrome are such as to be easily overlooked. It is the purpose of this paper to present the clinical and laboratory findings in eight cases of milk-alkali syndrome seen at the Mayo Clinic since 1949, in order to emphasize the hazards and relative clinical importance of this condition.

Medical literature is replete with references to untoward consequences of excessive alkali therapy, particularly in treatment of peptic ulcer, but these deal almost exclusively with the production of clinical alkalosis and its consequences. In 1936, Cope[5] reported four cases of alkalosis with hypercalcemia complicating the treatment of gastric ulcers with alkaline powders. Despite the very high blood levels of calcium, there was prompt return of the blood calcium to normal within 10 days following removal of the absorbable alkalis from the diet. Cope's patients were ingesting large amounts of calcium carbonate. The report of Burnett and co-workers,[1] previously referred to, was the first to call attention to hypercalcemia occurring in the absence of marked alkalosis. In all six of Burnett's cases there were conjunctival or corneal lesions as described previously by Walsh and Howard[6] in patients having hypercalcemia of various sorts. The conjunctival lesions were small glass-like particles in the conjunctiva near the palpebral fissures. The corneal changes consisted of hazy gray granular epithelial and subepithelial deposits running concentrically with the limbus on either the nasal or the temporal side or both.

Becker and colleagues[7] have recently reported renal parenchymal calcification of varying degree in 36% of 99 patients who had chronic active or healed duodenal ulcer. Sixty-eight per cent of these patients had a history of high intake of absorbable alkalis. Becker and colleagues postulated that these patients had received large amounts of calcium in the diet and had also suffered from asymptomatic and transient episodes of alkalosis.

Grant, in 1922,[8] described alkalosis occurring as a result of Sippy powders (calcium carbonate and magnesium oxide) in treatment of peptic ulcer. Later Hardt and Rivers[9] presented detailed observations on 16 patients in whom toxic symptoms developed while they were ingesting large amounts of absorbable alkalis. The significant symptoms noted were a distaste for milk, anorexia, nausea, vomiting, weakness, and clouding of the sensorium. Laboratory studies revealed elevation of the blood urea, a normal or elevated carbon-dioxide-combining power and

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* References 2-4.

varying quantities of albumin, casts, erythrocytes, and leucocytes in the urine. After omission of absorbable alkalis the symptoms rapidly disappeared, with gradual restoration of normal renal function. Many other observers have described similar findings.

Some difference of opinion has been expressed concerning the importance of antecedent renal damage in the development of alkalosis during treatment with alkaline powders. By estimating renal clearance of sulfate before and after recovery from alkalosis such as has been described, Wilkinson and Jordan [10] decided that antecedent renal damage had been present in most of their cases. Berger and Binger [11] stressed the importance of studying renal function in all patients for whom a Sippy regimen was contemplated. Kirsner and Palmer,[12] however, considered that alkalosis could appear in the absence of antecedent renal disease. They gave large amounts of absorbable alkalis to a number of patients who had impaired renal function, without the development of alkalosis. In cases in which alkalosis occurred, persistent diminution of renal function was not encountered, although diminished clearance of urea was demonstrated several months after alkalosis had disappeared.

McGee and his associates [18] gave 20 to 30 grains (about 1.3 to 2 gm.) of a mixture of calcium carbonate and magnesium oxide every hour from 7 a. m. to 9 p. m. for eight days to 17 subjects with normal kidneys. Although blood urea and carbon-dioxide-combining power did not change significantly, urea clearance fell 30% or more in 10 of the patients. Kirsner and Palmer [14] considered that hypochloremia and dehydration contributed to the production of alkalosis. They treated 27 patients in whom alkalosis had developed while the patients were taking calcium carbonate by administering sodium chloride and continuing the alkali. Clinical improvement was prompt in all 27 cases despite the continued use of calcium carbonate, with restoration of normal serum electrolytes in 7 to 14 days. Jeghers and Lerner [15] stressed, however, that vomiting with loss of chlorides is by no means a constant concomitant of alkalosis and reported several cases in which it was not present or developed only after the syndrome was manifest.

REPORT OF CASES

CASE 1.—A 43-year-old man registered at the clinic in April, 1953, complaining of recurrent epigastric pain and generalized weakness. He stated that gastric resection and vagotomy had been performed in 1950 for duodenal ulcer but that symptoms had recurred several weeks postoperatively. In March, 1953, a diagnosis of chronic nephritis had been considered because of persistent elevation of the blood urea. The patient estimated that he had been ingesting 1½ to 2 qt. (about 1.4 to 1.9 liters) of milk, one to two packages of a commercial antacid preparation, and 4 to 6 teaspoonfuls (about 15 to 22 cc.) of alkaline powders per day. These powders were a mixture of calcium carbonate, magnesium carbonate, and magnesium trisilicate.

The results of physical examination were not remarkable. The blood pressure was 140/90. The concentration of blood urea was 120 mg. per 100 cc.; carbon-dioxide-combining power, 22 mEq. per liter; hemoglobin, 11.3 gm. per 100 cc.; calcium, 13.7 mg. per 100 cc.; inorganic phosphate, 2.6 mg. per 100 cc., and alkaline phosphatase, 2.7 Bodansky units. Roentgenograms of the urinary tract appeared normal. No ocular deposits of calcium were observed. A second determination of serum calcium measured 12.8 mg. per 100 cc.

The urine had a specific gravity of 1.014 and an acid reaction and contained in addition numerous casts and a few erythrocytes and leucocytes. Albuminuria was graded 2 on a basis of 1 to 4.

The patient was placed on a quantitative diet which contained 135 mg. of calcium per day. During the first 24-hour period 259 mg. of calcium were excreted in the urine, but only 110 mg. of calcium were found in the second 24-hour urine specimen and 96 mg. in the third 24-hour urine specimen. A gastrojejunal ulcer was suspected clinically, but it could not be confirmed by roentgenographic studies of the gastrointestinal tract. The hypercalcemia was considered to be secondary to the large intake of milk and absorbable alkalis. The patient was placed on a liberal ulcer diet containing no dairy products. An antacid (aluminum hydroxide gel) was prescribed for intermeal feedings.

Ten days later the level of serum calcium was 8.8 mg. per 100 cc. and urea was 42 mg. per 100 cc. Urinalysis disclosed a specific gravity of 1.006, a trace of albumin, and no sediment other than an occasional erythrocyte. The gastrointestinal symptoms were completely relieved. The patient was dismissed on a liberal ulcer diet without dairy products.

During a check-up, in August, 1953, four months later, the patient stated he felt well, had no epigastric distress, and was carrying on full-time employment. On this occasion, the urine contained an occasional erythrocyte and a trace of albumin. The blood urea and calcium remained normal.

CASE 2.—A 52-year-old man registered at the clinic on Oct. 8, 1951. He described recurrent epigastric pain and melena. A diagnosis of duodenal ulcer had been made in 1930, when a crater had been demonstrated by fluoroscopic examination. He drank 1 to 2 qt. (about 0.9 to 1.9 liters) of milk daily and used about 1 lb. (about 0.5 kg.) of alkaline powders per week. The powders contained calcium carbonate and magnesium carbonate.

On examination the blood pressure was 154/96. The results of physical examination were otherwise negative. The hemoglobin measured 12.4 gm. per 100 cc.; urea, 94 mg. per 100 cc.; calcium, 12.1 mg. per 100 cc., and inorganic phosphate, 2.8 mg. per 100 cc. The urine had a specific gravity of 1.006, an alkaline reaction, and no albumin or sediment. An excretory urogram showed no evidence of nephrocalcinosis or renal calculi. Examination of the eyes revealed no calcium deposits. No urinary studies of calcium excretion were made.

A liberal ulcer diet low in calcium content was prescribed. On the 12th day partial gastrectomy was performed. The postoperative course was uneventful. On the day of dismissal the blood urea was 48 mg. per 100 cc. and calcium was 9.4 mg. per 100 cc.

The patient returned for examination in January, 1953. He had no gastrointestinal symptoms. The blood pressure was 130/85. The results of urinalysis were entirely normal. The blood urea remained slightly elevated, 48 mg. per 100 cc. The results of all other blood studies were normal.

CASE 3.—A man aged 49 years was admitted in critical condition in August, 1953, with intractable nausea and vomiting, which had been present for several weeks.

The patient was conspicuously dehydrated, and his blood pressure measured 80/60. Examination of the ocular fundi disclosed minimal narrowing of retinal arterioles. The results of physical examination were otherwise essentially normal. Blood urea measured 234 mg. per 100 cc.; creatinine, 14 mg. per 100 cc.; sulfate, 44.5 mg. per 100 cc.; chlorides, 61.5 mEq. per liter; carbon-dioxide-combining power, 41.2 mEq. per liter; calcium, 12.9 mg. per 100 cc.; inorganic phosphates, 4.8 mg. per 100 cc.; potassium, 2.9 mEq. per liter, and alkaline phosphatase, 3.2 Bodansky units. A urine specimen had specific gravity of 1.013, an acid reaction, numerous pus cells, and an occasional erythrocyte. Albuminuria was graded 2 on a basis of 1 to 4.

Initial treatment included intravenous infusions of isotonic sodium chloride solution and 5% solution of dextrose, to which was added potassium chloride. Within 24 hours vomiting had stopped and the patient's condition was improved. He was then able to give a history of recurrent burning epigastric distress occurring 30 to 60 minutes after meals, occasionally between meals, and rarely at night. This had been present over a period of 25 years. Because of a distaste for milk he seldom drank more than one glass (about 240 cc.) daily. Twenty years previously Sippy powders containing calcium carbonate and magnesium oxide had been prescribed, and he estimated his average intake of powders to be 2½ lb. (about 1.1 kg.) per week during much of the interim. He denied ingestion of vitamin D. Several renal calculi had been passed in 1948. A diagnosis of chronic nephritis had been made in 1951, because of recurrent nausea and vomiting and elevation of blood urea.

The patient was placed on a strict ulcer diet employing milk substitutes and aluminum hydroxide gel. All absorbable alkalis were withheld; improvement occurred rapidly. Blood calcium returned to a normal value of 9.1 mg. per 100 cc. on the fifth day, at which time hypochloremia, hypokalemia, and alkalosis had also been corrected. On the 10th day the blood urea was 58 mg. per 100 cc.; the blood creatinine was 2.4 mg. per 100 cc.; sulfates, 4.8 mg. per 100 cc.; calcium, 9.5 mg. per 100 cc., and inorganic phosphate, 2.5 mg. per 100 cc. The urine was normal at the time of dismissal.

CASE 4.—A man aged 39 years was admitted on Dec. 19, 1952, complaining of recurrent bouts of midepigastric pain which had recurred for seven years and of mild polyuria and dysuria of six months' duration. In 1946, roentgenograms had disclosed a crater in the first portion of the duodenum. Three weeks prior to admission melena had been noted for the first time. The patient drank ½ pt. to 1 qt. (about 236 to 946 cc.) of milk and used 3 to 4 teaspoonfuls (about 11 to 15 cc.) of baking soda and one to two packages of a commercial antacid preparation each day. There was no history of previous renal disease.

The results of physical examination were not remarkable except for blood pressure of 150/105. The blood urea was 116 mg. per 100 cc.; calcium, 11.8 mg. per 100 cc.; inorganic phosphate, 3.2 mg. per 100 cc.; hemoglobin, 13.4 gm. per 100 cc., and alkaline phosphatase, 2.7 Bodansky units. A urine specimen had a specific gravity of 1.009 and an acid reaction and contained an occasional erythrocyte and leucocyte. Albuminuria was graded 2 on the basis of 1 to 4. During a three-day period during which the patient followed a quantitative diet containing 135 mg. of calcium per day, urinary excretion of calcium in the urine did not exceed 126 mg. per 24 hours. An excretory urogram disclosed a small calculus

in the right kidney. No calcium deposits were observed in the eyes.

After three days of a liberal ulcer diet low in calcium, the blood calcium measured 9.9 mg. per 100 cc.; urea, 100 mg. per 100 cc., and carbon-dioxide-combining power, 24 mEq. per liter. Ten days later the urea was 52 mg. per 100 cc. and calcium was 10.3 mg. per 100 cc. A urine specimen on this occasion had a specific gravity of 1.009 and an acid reaction and contained a trace of albumin.

The patient returned in February, 1953. Only minimal symptoms of ulcer had occurred so long as he followed the prescribed diet. Polyuria was no longer a problem. Blood urea now measured 66 mg. per 100 cc.; carbon-dioxide-combining power, 23 mEq. per liter; calcium, 10.2 mg. per 100 cc., and inorganic phosphate, 3.3 mg. per 100 cc.

CASE 5.—A man aged 49 years was admitted on Nov. 22, 1952. He had had recurrent distress from a chronic duodenal ulcer for a period of six years. Roentgenograms in 1946 had revealed a crater, and the ulcer had perforated in 1949. His average ingestion of milk had varied from 1 to 4 qt. (about 0.9 to 3.8 liters) daily. In the six months preceding admission he stated that he had been virtually "living on milk and alkaline powders." He generally took 10 to 12 teaspoonfuls (about 37 to 44 cc.) daily of a powder consisting of a mixture of calcium carbonate, magnesium carbonate, and sodium bicarbonate.

The results of physical examination were essentially negative except for a blood pressure of 168/100. Blood urea measured 102 mg. per 100 cc.; chlorides, 89.1 mEq. per liter; carbon-dioxide-combining power, 22 mEq. per liter; potassium, 3.8 mEq. per liter; calcium, 15.6 mg. per 100 cc.; inorganic phosphate, 3.8 mg. per 100 cc., and alkaline phosphatase, 3.5 King-Armstrong units. The urine had a specific gravity of 1.008, an acid reaction, and no albumin and contained an occasional erythrocyte or leucocyte. Urologic evaluation revealed no nephrocalcinosis or renal calculi. Studies with a slit lamp disclosed no ocular deposits of calcium. No quantitative estimate of calciuria was made.

A strict ulcer diet without milk products and without absorbable alkalis was prescribed. Seven days later the serum calcium measured 11.4 mg. per 100 cc. and urea was 52 mg. per 100 cc. Subtotal gastrectomy and duodenectomy were performed on Dec. 4, 1952. Subsequently, on Dec. 8, 1952, the serum calcium measured 9.9 mg. per 100 cc.; carbon-dioxide-combining power, 21 mEq. per liter, and inorganic phosphate, 2.5 mg. per 100 cc. The urine had a specific gravity of 1.008, an acid reaction, and an occasional erythrocyte on microscopic examination. Postoperative recovery was uneventful.

CASE 6.—A man aged 47 years registered at the clinic on Sept. 22, 1950, with a complaint of recurrent bouts of epigastric pain. His first symptoms had occurred in 1935, when a duodenal ulcer was identified by roentgenographic examination. He followed a strict ulcer diet and used Sippy powders for one year, with complete relief of symptoms. He remained free of discomfort until 1948, when all of his distress recurred. For two years thereafter he consumed about 2 oz. (about 57 gm.) of baking soda and 1 to 2 qt. (about 0.9 to 1.9 liters) of milk each day. During the four weeks preceding admission he had been vomiting two or three times a day. In May, 1950, he had been told by his family physician that his kidneys contained calcium.

There were no significant findings on physical examination except for a blood pressure of 164/106. The blood urea was 100 mg. per 100 cc.; chlorides, 73.9 mEq. per liter; carbon-dioxide-combining power, 39.4 mEq. per liter; calcium, 11.2 mg. per 100 cc.; inorganic phosphate, 3.4 mg. per 100 cc.; alkaline phosphatase, 4.2 Bodansky units, and hemoglobin, 14.5 gm. per 100 cc. A urine specimen had a specific gravity of 1.012, an alkaline reaction, and no albumin and disclosed moderate hematuria. An excretory urogram disclosed bilateral renal calculi.

A strict ulcer diet low in calcium was prescribed, in addition to intravenous infusions of isotonic sodium chloride solution and 5% dextrose in saline solution. Four days later blood chlorides measured 94 mEq. per liter, the carbon-dioxide-combining power was 28 mEq. per liter, and blood urea was 65 mg. per 100 cc. On the 15th hospital day posterior gastroenterostomy was performed. The postoperative course was uneventful. Prior to dismissal, studies revealed a blood urea of 30 mg. per 100 cc.; calcium, 9.1 mg. per 100 cc.; inorganic phosphate, 2.8 mg. per 100 cc., and normal chlorides and carbon-dioxide-combining power. At the time of dismissal the patient was advised to follow a liberal ulcer diet without milk or dairy products and to take aluminum hydroxide gel between meals and at bedtime.

The patient returned in July, 1951, free of ulcer symptoms. The serum calcium at this time measured 9.2 mg. per 100 cc. and the blood urea was 44.0 mg. per 100 cc. The results of urinalysis were negative except for a specific gravity of 1.011 and an occasional erythrocyte.

CASE 7.—A 51-year-old woman registered at the clinic on Dec. 15, 1953, because of intractable ulcer pain. Symptoms of ulcer had been noted intermittently for 20 years, but during the past year distress had been continuous and nocturnal pain had been a conspicuous feature. Vomiting was present only when self-induced. In May, 1953, the patient had experienced a severe right renal colic, and it was considered that she had passed a kidney stone.

She ingested 1 qt. (about 946 cc.) of milk and 1 pt. (about 473 cc.) of half cream, half milk each day. Sippy powders, containing calcium carbonate and magnesium oxide, had been used intermittently for years, with an average intake of three to six powders daily in the past two years, together with a proprietary antacid preparation and about ½ lb. (about 227 gm.) of baking soda each month. She had complained bitterly of a metallic taste for the past two months.

Physical examination disclosed slight epigastric tenderness and a blood pressure of 180/160. Blood urea was 126 mg. per 100 cc.; chlorides, 83.5 mEq. per liter; carbon-dioxide-combining power, 29 mEq. per liter; calcium, 13.6 mg. per 100 cc.; inorganic phosphate, 6.2 mg. per 100 cc.; potassium, 5.5 mEq. per liter, and alkaline phosphatase, 11.5 King-Armstrong units. The urine had a specific gravity of 1.008, an alkaline reaction, and a few erythrocytes and leucocytes. Albuminuria was graded 1 on the basis of 1 to 4. There were no ocular deposits of calcium.

The patient was placed on a strict ulcer diet containing approximately 200 mg. of calcium daily. Clinical improvement occurred promptly, and within two days the serum calcium had dropped to 10.7 mg. per 100 cc. On the sixth hospital day the serum calcium value was 9.4 mg. per 100 cc. Fourteen days after admission, partial gastrectomy and duodenectomy were performed. Preoperative studies revealed a blood urea of 26 mg. per 100 cc.; calcium, 8.4 mg. per 100 cc., and normal chlorides and carbon-dioxide-combining power. An excretory urogram was negative. The urea clearance was 19 cc. per minute, with a urine flow of 0.7 cc. per minute. The results of preoperative studies of urinary excretion of calcium wer normal. A needle biopsy specimen from a kidney was obtained during operation. This revealed focal calcification in the renal tubules.

The patient's postoperative course was uncomplicated. On the day of dismissal, blood urea was 48 mg. per 100 cc.; calcium, 10.2 mg. per 100 cc., and inorganic phosphate, 3.6 mg. per 100 cc. The urine had a specific gravity of 1.008 and an alkaline reaction. Albuminuria was graded 1. The urea clearance following operation was 15.1 cc. per minute, with a urine volume of 0.7 cc. per minute.

CASE 8.—A 36-year-old man was admitted on March 19, 1954, complaining of severe persistent epigastric pain which extended into the interscapular region. He had been vomiting several times a day for the past four weeks. His symptoms had started in the summer of 1950. Milk and alkalis had provided only temporary relief. It was stated that the results of exploration of the abdomen in February, 1951, had been negative and that postoperatively the patient had continued to have recurrent episodes of pain despite an ulcer diet. It was also stated that reexploration of the abdomen in 1953 had revealed "adhesions." His symptoms had persisted, and subsequently opiates had been required to relieve the pain. His consumption of milk averaged 2 to 3 qt. (about 1.9 to 2.8 liters) daily. He was using four to six proprietary antacid tablets daily. No history of antecedent renal disease or renal calculi could be elicited.

The results of physical examination were not remarkable except for marked epigastric tenderness. The blood pressure was 150/115. Studies with the slit lamp revealed superficial deposits resembling calcium in both corneas. Blood urea was 85.4 mg. per 100 cc.; carbon-dioxide-combining power, 23 mEq. per liter; potassium, 4.3 mEq. per liter; sulfates, 7.3 mg. per 100 cc.; calcium, 12.8 mg. per 100 cc.; serum inorganic phosphorus, 3.8 mg. per 100 cc., and alkaline phosphatase, 11 King-Armstrong units. The following day the calcium was 11.9 mg. per 100 cc. and urea 80 mg. per 100 cc., with a urea clearance of 13.6 cc. per minute and a urine flow of 1.5 cc. per minute. Roentgen rays revealed an ulcer crater in the duodenum. The urine had a specific gravity of 1.008, an acid reaction, and a few erythrocytes. Albuminuria was graded 2 on a basis of 1 to 4.

On March 27, 1954, a strict ulcer diet low in calcium content was prescribed. All absorbable alkalis were discontinued. On March 29 the serum calcium was 10.6 mg. per 100 cc. and urea 46 mg. per 100 cc. During a three-day study period, the excretion of calcium in the urine did not exceed 136 mg. in 24 hours. On April 2 the serum calcium had dropped to 9.6 mg. per 100 cc. and urea to 42 mg. per 100 cc. On April 5, 1954, posterior gastroenterostomy and transabdominal vagotomy were performed. The patient's postoperative course was uneventful, and he was completely relieved of his symptoms.

COMMENT

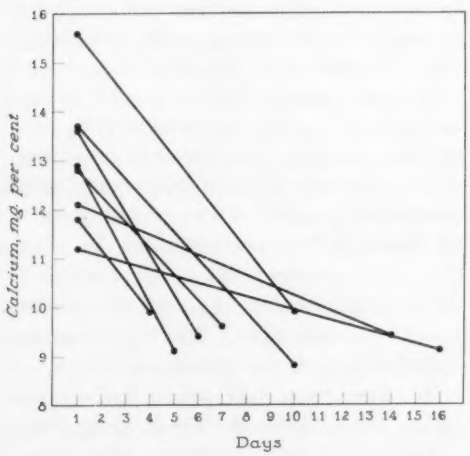
The cases which have just been described in detail correspond in every important respect to those previously outlined by Burnett and co-workers. The clinical symptoms with pertinent laboratory findings seen in these patients are summarized in the Table. Also summarized are the estimated quantities of milk and absorbable alkalis which were ingested in each case. The number of days required for the blood calcium to return to normal levels following the use of an ulcer diet low in calcium content is shown in the Figure.

The syndrome characterized by the foregoing cases must be differentiated from other conditions accompanied by hypercalcemia and azotemia, such as hypervitaminosis D,

Pertinent Data of Milk and Alkali Intake as Well as Significant Laboratory Findings

Case	Duration of Ulcer Symptoms, Yr.	Blood Findings on Admission: Serum Calcium, Mg./100 Cc.	Blood Findings on Admission: Serum Inorganic Phosphorus, Mg./100 Cc.	Blood Findings on Admission: Blood Urea, Mg./100 Cc.	Blood Findings on Admission: CO_2-Combining Power, mEq./L.	Milk per Day	Absorbable Alkali
1	20	13.7	2.6	120	22	1½-2 qt.	1. Alkaline powders (calcium carbonate, magnesium carbonate, and magnesium trisilicate) 4-6 teaspoonfuls/day 2. Proprietary antacid 1-2 packages/day
2	22	12.1	2.8	94	..	1-2 qt.	1. Alkaline powders (calcium carbonate and magnesium carbonate) 1 lb./wk.
3	25	12.9	4.8	234	41.2	1-2 glasses	1. Sippy powders (calcium carbonate and magnesium oxide) 2-2½ lb./wk.
4	7	11.8	3.2	116	..	½ pt.-1 qt.	1. Sodium bicarbonate 3-4 teaspoonfuls/day 2. Proprietary antacid 1-2 packages/day
5	6	15.6	3.8	102	22	1-4 qt.	1. Alkaline powders (calcium carbonate, magnesium carbonate, and sodium bicarbonate) 10-12 teaspoonfuls/day
6	2	11.2	3.4	100	39.4	1-2 qt.	1. Sodium bicarbonate 1 lb./wk.
7	20	13.6	6.2	126	29	1 qt.; 1 pt. of half milk and half cream	1. Sippy powders (calcium carbonate and magnesium oxide) 3-6/day 2. Sodium bicarbonate ½ lb./mo. 3. Proprietary antacid 1 package every other day
8	3	12.8	3.8	85.4	23	2-3 qt.	1. Proprietary antacid 4-6 tablets/day

primary hyperparathyroidism, multiple myeloma, sarcoidosis, and carcinomatosis of bone. A history of ingesting vitamin D will most readily identify cases in the first category; the character and extent of the osseous involvement, together with other specific features, will, in the majority of instances at least, easily differentiate the others. Primary hyperparathyroidism without bone disease, however, may provide a difficult problem in differential diagnosis. This is especially the case when, as not infrequently happens, primary hyperparathyroidism occurs in a patient who has active peptic ulcer.



Time required for blood calcium to return to normal following the use of a diet low in calcium.

The distinction between primary hyperparathyroidism without bone disease occurring in a patient with active peptic ulcer, on the one hand, and milk-alkali syndrome, on the other hand, becomes even more difficult in those instances (unfortunately all too common) in which, because of secondary nephrocalcinosis or pyelonephritis resulting from nephrolithiasis, primary hyperparathyroidism is also accompanied by significant azotemia. In these circumstances there may result a fall in serum calcium from the previously high levels to levels more nearly normal. The serum phosphorus usually rises from the pathologically low levels to normal or even elevated levels. There is, furthermore, a disappearance of the hypercalciuria which ordinarily characterizes primary hyperparathyroidism. Thus, the occurrence of renal insufficiency tends to mask each of the primary chemical features of this disease. In most circumstances, however, even though some degree of renal impairment with nitrogen retention is present in primary hyperparathyroidism, both hypercalciuria and hypercalcemia persist.

Burnett and associates stressed the lack of hypercalciuria as a critical diagnostic feature

of the milk-alkali syndrome and as a characteristic of most importance in differentiating it from primary hyperparathyroidism. This was true of the cases which we have described. However, the relative degree to which these diagnostic features may vary in these two conditions remains to be precisely defined. The difficulties of differential diagnosis are emphasized by the following illustrative case.

Report of Case Illustrating Difficulties of Differential Diagnosis.—A man 51 years of age was admitted to the hospital April 12, 1951, with a history of recurrent epigastric pains over a period of 28 years. These were attributed to a chronic duodenal ulcer. Melena had been noted on two previous occasions. For many years the patient had taken 1 oz. (about 28 gm.) of baking soda and 6 to 7 gm. of calcium carbonate daily in addition to frequent doses of various proprietary antacid powders and 3 to 4 qt. (about 2.8 to 3.8 liters) of milk.

The blood pressure was 160/90. There were a thyroidectomy scar and a firm adenoma in the left lobe of the thyroid gland. The blood urea was 78 mg. per 100 cc.; chlorides, 103 mEq. per liter; calcium, 13.1 mg. per 100 cc.; inorganic phosphates, 4.3 mg. per 100 cc., and alkaline phosphatase, 5.5 Bodansky units. The hemoglobin measured 12.9 gm. per 100 cc. of blood. The urine had a specific gravity of 1.006 and an acid reaction and contained a trace of albumin and an occasional erythrocyte and leucocyte. On a second determination serum calcium was 13.6 mg. per 100 cc. and inorganic phosphorus was 4.0 mg. per 100 cc. No calcium deposits were present in the eyes. A rontgenogram of the kidneys, ureters, and bladder did not disclose any calculi. A roentgenogram of the gastrointestinal tract revealed the crater of a large duodenal ulcer.

The patient was placed on a quantitative diet containing 135 mg. of calcium per day. During the first 24-hour period 222 mg. of calcium was excreted in the urine; 247 mg. appeared during the second 24-hour period, and 186 mg., in the third 24-hour period. These values were considered to represent excessive calciuria. The quantitative low-calcium diet was continued for 10 days, without effect on the patient's condition or his calcium level. At the end of that time the serum calcium measured 13.9 mg. per 100 cc. and the inorganic phosphorus, 3.8 mg. per 100 cc.

A clinical diagnosis of primary hyperparathyroidism was made, and cervical exploration for parathyroid tumor was carried out May 2, 1951. A large adenoma of the left lobe of the thyroid was removed, but no parathyroid tumor was found. Postoperatively, serum calcium varied between 13.1 and 12.3 mg. per 100 cc. Since primary hyperparathyroidism was still considered the most likely diagnosis, exploration of the mediastinum was advised, but this advice was refused by the patient. He was therefore dismissed on a liberal ulcer diet without milk or milk products. His diet contained approximately 250 mg. of calcium daily. All absorbable alkalis were discontinued.

The patient returned for further consideration in September, 1951, at which time the serum calcium had dropped to 9.9 mg. per 100 cc., while the inorganic phosphorus was 3.1 mg. per 100 cc. and urea, 52 mg. per 100 cc. His ulcer had been quiescent during the interval.

Because of a recurrence of ulcer symptoms, the patient returned, in December, 1951, for gastric operation. Preoperatively the blood calcium was 10.4 mg. per 100 cc. and urea, 54 mg. per 100 cc.; blood pressure was now 120/85. Partial gastrectomy and duodenectomy were performed, with an uneventful postoperative course. Prior to dismissal the blood calcium was 9.7 mg. per 100 cc. and inorganic phosphorus was 3.4 mg. per 100 cc. The urine had a specific gravity of 1.008, an acid reaction, and a few leucocytes. Albuminuria was graded 2 on a basis of 1 to 4.

Comment on Preceding Case.—It must be considered that the existence of an active duodenal ulcer in the presence of azotemia, hypercalcemia, negative results of exploration for parathyroid tumor, and restoration of normal serum calcium values after six months of therapy with a low-calcium diet provides a considerable basis for a diagnosis of milk-alkali syndrome in this case. However, the patient had pronounced hypercalciuria and failed to respond to fluids and to a calcium-poor regimen with the celerity which characterized the other cases which have been described. On this account, it must be considered that the patient may actually have had primary hyperparathyroidism after all. If this is assumed, the subsequent development of a normal serum calcium must be attributed to some such event as the infarction of the undiscovered tumor, perhaps by the consequences of the surgical procedure which was performed. Neither alternative —that is, a milk-alkali syndrome which was both refractory to therapy and accompanied by an unusually severe hypercalciuria or a self-curing primary hyperparathyroidism— provides a very satisfying answer or expla-

nation for this case, particularly since the circumstances are such that neither diagnosis can be proved or disproved.

Further Diagnostic Considerations.—The diagnosis of hypervitaminosis D hinges on a careful evaluation of the history with respect to the ingestion of vitamin D. Hypervitaminosis D is accompanied by hypercalcemia resulting from increased absorption of calcium and phosphorus from the gastrointestinal tract. There may also be some mobilization of calcium from the skeleton. Hypercalciuria results and leads to renal damage, nephrocalcinosis, azotemia, and retention of phosphates and, ultimately, to widespread metastatic calcification if the process is permitted to continue. The interval required for the serum calcium to return to normal following omission of vitamin D varies from days to weeks and in some cases may take many months. In many patients the serum calcium may return to normal within 7 to 10 days following omission of vitamin D. Thus, circumstances can easily be imagined in which milk-alkali syndrome and hypervitaminosis D might readily become confused. On the other hand, we have observed some instances of hypervitaminosis D in which four to six months elapsed following removal of vitamin D from the diet before the serum calcium was restored to normal.

Because of the occurrence of azotemia, a diagnosis of chronic nephritis was made in three of the cases which we have reported. However, chronic nephritis is ordinarily associated with hypocalcemia, hyperphosphatemia, and a metabolic acidosis when azotemia has once begun. A history of clear-cut renal disease preceding this episode could not be elicited in any of the cases, but neither could it be entirely excluded. The extraordinary rapidity with which renal function improved and azotemia disappeared in most of the cases once milk and absorbable alkalis were withheld constitutes the most striking feature of the milk-alkali syndrome. Improvement appeared to be relatively complete in three of the patients, but in the remaining five cases some elevation of blood urea and some abnormality of the results of urinalysis appeared to persist after other signs and symptoms of the malady had disappeared. It is difficult to be sure just what comes first in the milk-alkali syndrome. Impaired renal function with decreased excretion of calcium by the kidneys may be responsible for the situation. On the other hand, it is possible that the mechanism involved may be due to some fundamental disturbance of calcium metabolism, with the renal insufficiency and its concomitants secondary to the hypercalcemia, as is the case in hyperparathyroidism and hypervitaminosis D. Against this explanation is the apparently critical fact that hypercalciuria is characteristically lacking in instances of milk-alkali syndrome.

Vomiting, dehydration, and hypochloremia, as stressed by Kirsner and Palmer, may play a role in some cases but cannot account for impaired renal function in most of the cases. Significant alkalosis was noted only in those patients (Cases 3, 6, and 7) who had been vomiting and were dehydrated on admission.

The condition which has been described would appear important to recognize for two principal reasons: (1) in order to differentiate it from cases of primary hyperparathyroidism so as to avoid unnecessary and useless surgical exploration in patients suspected of the latter condition and (2) to recognize the occurrence of a serious and possibly fatal renal lesion complicating the treatment of duodenal ulcer which, at the very least, must seriously aggravate surgical risk.

It is probably desirable also to add a word of caution regarding the management of patients who have duodenal ulcer nowadays, when so many very effective antacid measures not employing absorbable alkalis are available. Sippy powders and other absorbable alkalis still have numerous adherents and are still widely used. Still more widely used, of course, are various proprietary antacid preparations. In patients who are suffering from chronic or intractable ulcer pain the temptation to use such preparations in large and possibly excessive amounts may

continue to be a serious hazard in some cases. So long as this is the case, it remains a matter of considerable importance for the internist to be on the alert for the signs and symptoms of hypercalcemia which may arise as a result of such excessive use of absorbable alkalis as well as the more familiar symptoms of alkalosis, which have long been recognized as arising therefrom.

SUMMARY

The clinical and laboratory findings in eight cases of so-called milk-alkali syndrome are summarized. The syndrome is characterized by hypercalcemia, renal insufficiency, and azotemia and, occasionally, by alkalosis. The condition appears to be distinguishable from primary hyperparathyroidism by the absence of hypercalciuria and because of the rapidity with which the azotemia and hypercalcemia disappear on omission of milk and antacids containing absorbable alkalis. The features of this condition as they relate to the differential diagnosis of calcium disorders and to the management of patients having duodenal ulcer are discussed.

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Angiokeratoma Corporis Diffusum Universale (Fabry)

First American Report of a Rare Disorder

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We recently had the opportunity to study a patient with a rare condition hitherto unrecognized in American literature and one that may be readily confused with other disorders, especially purpura and hereditary telangiectasia. This led us to review the literature concerned with a form of "angiokeratoma" first described by Fabry in 1898 under the title of "purpura hemorrhagica nodularis" and more recently claimed in European reports to represent a systemic condition.

HISTORICAL REVIEW

The term "angiokeratoma" was introduced by Mibelli * to designate small raised partially hyperkeratotic vascular aneurysms in the skin of the extensor surfaces of the distal phalanges of the hands and feet and, more rarely, of other exposed areas of the body. The lesion Mibelli described is associated with exposure to cold and chilblains. The same term has been used to designate somewhat similar lesions occurring mainly over the scrotum in elderly persons; this is the so-called angiokeratoma scroti, originally described by Fordyce.†

In 1898, J. Fabry [2] described the case of a 13-year-old boy who, at the age of 9, showed evidence of a peculiar skin disorder: small painless dark nodules in the left popliteal fossa, which, in the course of the following years, appeared on many other parts of the body. At the time of examination, innumerable minute, bluish-red to almost black, slightly raised dots were found in thick groups on the iliosacral region, the scrotum, the posterior aspect of the thighs, the umbilicus, the anterior chest, and, in smaller groups, on the extensor surfaces of the lower extremities and the entire surface of the upper extremities. A few lesions were also present on the buccal mucosa. The physical examination was otherwise negative except for slightly edematous eyelids. Seventeen years later [3] it was apparent that the lesions had become more numerous but their distribution was essentially the same. The patient appeared relatively well except for some asthmatic symptoms. There had been no bleeding manifestations. His eyelids were slightly swollen, and albumin was found in the urine. Sections of the skin lesions were initially interpreted as showing hemorrhages, but aneurysms of the smaller vessels of the cutis and subcutis were also noticed; the stratum corneum was hypertrophic in many places but not in all. Fabry added little new information in a follow-up in 1930.[4] His patient had died two years previously, presumably from a pulmonary disease. Since 1915 [5] Fabry had considered this case to be one of "angiokeratoma corporis diffusum (universale)."

Eight similar cases were described in the course of the next quarter century.‡ Albuminuria was noted in the cases of Anderson [6] and of Steiner and Voerner.[7] Pain,

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* Mibelli: Gior. ital. mal. ven. **24**:285, 1889, cited by Traub and Tolmach.[1]

† Fordyce: J. Cutan. Dis. **14**:81, 1896, cited by Traub and Tolmach.[1]

‡ References 6-11.

flushing, and numbness of the extremities in warm weather were also troublesome in the latter case; at low temperatures the patient's extremities felt ice-cold. He also complained of urinary frequency, diminished sweating, palpitation, headache, and weakness.[8] Fundoscopy revealed engorgement of the veins and thickening of the walls of the smaller retinal arteries. Granular casts were found on one occasion. These authors were probably the first to suspect that they were dealing with a systemic disorder, not simply a local skin affliction.

Sibley's patient [10] resembled the case of Steiner and Voerner in that he suffered from pains in the hands and feet and his joints were enlarged and painful. The second aortic sound was accentuated, but the blood pressure was not recorded. Urinalysis revealed a specific gravity of 1.004 and albuminuria; no casts or pus were present in the sediment, but "fat cells" were described.

A familial occurrence of the disorder was suggested by the observations of Stümpke [9] and Weicksel.[11] The former described the disorder in three brothers; the latter, in two brothers. Of interest also were the findings in the eyes in Weicksel's cases: broadening and varicosities of the vessels on the bulbar and palpebral conjunctivae, marked tortuosity and variation in the caliber of the retinal vessels, and opacities in the cornea. These spared the center and assumed a radiating distribution.

The reports of additional cases which followed § added little of interest, but that of Ruiter and Pompen [17] once again drew attention to the familial and the possibly systemic nature of the disorder. In three brothers, pains and cramps in the extremities aggravated by heat and decreasing in the cold, disturbance of sweating, persistent edema of the lower extremities, elevation of blood pressure, cardiac enlargement, and albuminuria were noted. Red corpuscles, leucocytes, and occasional casts were found in the urinary sediment. The authors did not regard the edema as being of cardiac or renal origin but assumed that its pathogenesis was related to vascular changes. They considered that there might be some connection between the skin lesions and the cardiac, vascular, and renal manifestations.

In 1947, the same authors, in collaboration with Wyers, reported a follow-up of one of the patients they had described in 1939 and added another unrelated case, with autopsy findings on both.[18] These are the first autopsies reported in cases of angiokeratoma corporis diffusum. Both patients had died in uremic coma. The new patient had presented the same symptoms and clinical and laboratory findings as had their original cases. At this time the two surviving brothers were reexamined and were found to have corneal opacities.

The essentials of the pathological investigation which were common to both cases were thickening of the media of the blood vessels as the result of accumulation of hyaline material between the muscle fibers and hypertrophy and pronounced vacuolization of the cytoplasm of the muscle fibers themselves. These changes were more pronounced in the medium- and larger-sized renal arteries than elsewhere but were also present in the vascular system of other organs (heart, lungs, liver, and spleen). Similar enlargement and paranuclear vacuolization were seen in the cardiac muscle fibers, which sometimes had a tubular appearance on cross section. Staining for glycogen and fat gave negative results. Thus, it was not possible to ascertain the nature of the substance in the vacuoles. In addition, the kidneys, small in both cases, displayed various degrees of hyalinization and sclerosis of the glomeruli as well as dilatation or atrophy of the renal tubules. The spleen contained large quantities of iron pigment. The skin lesions were similar to those of previously described cases.

Ruiter and his associates suggested that the skin lesions of angiokeratoma corporis diffusum universale may be a sign of an unknown internal disease and considered the possibility that they were dealing with a congenital metabolic disturbance in the mus-

§ References 12-16.

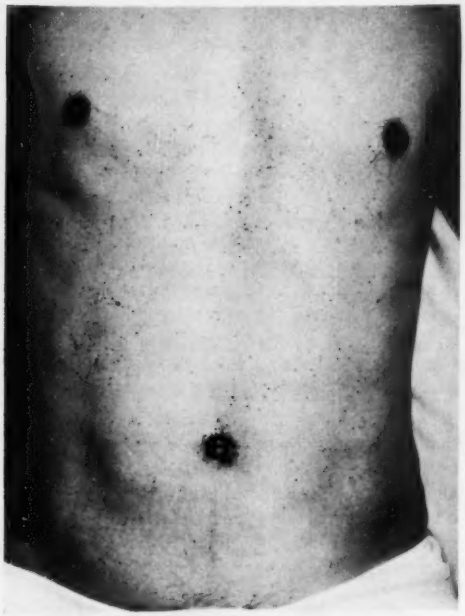


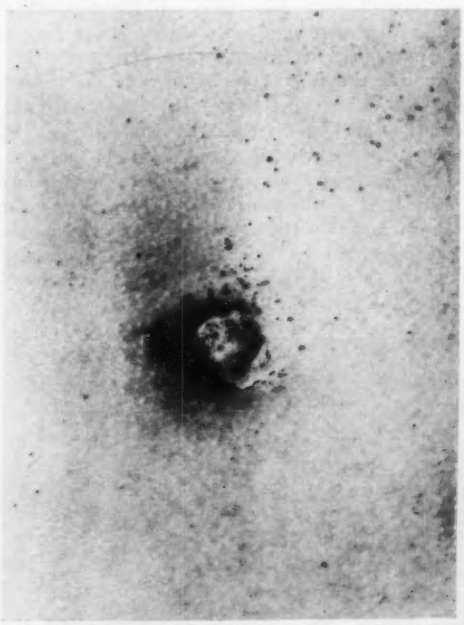
Fig. 1.—Angiokeratomas on chest and abdomen of Patient D. B. B.

cle cells of the heart and vessels. They also suggested that this might be a storage disease.

In 1950 [20] and subsequently in a series of papers || Hornbostel, Spier, Koch, and Scriba reported two cases of angiokeratoma corporis diffusum universale (Fabry) which, in the main, resembled those presented by Ruiter and his associates. Their contribution consisted in an extensive pathological investigation of the autopsy material in one case. The vascular and the myocardial changes described by Ruiter and co-workers were again found. However, Scriba [21] demonstrated that the vacuolization of these cells was due to the presence of a substance which showed birefringence under polarized light. Similar, doubly refractile substances were present in the spleen, the adrenals, and the lymph nodes and in several groups of ganglion cells of the brain and the peripheral nervous system. Chemical analysis of the cardiac muscle demonstrated the presence of 10 times the normal amount of diaminophosphatides, which differed, however, from typical sphingomyelin. On the basis of these findings, these investigators postulated that a hitherto undescribed lipoid-storage disease is the basic abnormality in this syndrome. Hornbostel and co-workers were able to make the diagnosis in their second case (previously diagnosed as a form of angiokeratoma Mibelli) on the basis of the biopsy of the skin, which showed the birefringent material in the media of the subcutaneous arteries.[25]

The most recent report,[26] that of Brown and Milne, is of interest because the diffuse angiokeratoma was observed in two half-brothers, born of the same mother but of different fathers. In both cases health and physical development were below normal and there was evidence of vascular disturbance in the form of acroparesthesiae. At the age of 30 one of the brothers developed an acute cerebral disturbance, which was considered to be vascular in origin. The spleen was felt 3 cm. below the costal margin, and there was mild hypochromic anemia which responded to iron therapy.

Fig. 2.—Distribution of the lesions about the umbilicus in Patient D. B. B. It can be seen that many are slightly raised. The variation in size is also noteworthy.



|| References 21-25.

Fig. 3.—Lesions over the buttocks in Patient D. B. B.

REPORT OF A CASE

In April, 1953, a 35-year-old male grocery clerk (D. B. B., C. M. 4550, S. L. G. H. 1997-53) was referred to us because of "purpura," anemia, and albuminuria. He had been rejected from army service twice because of purpura hemorrhagica. Since early youth, small red spots had been present all over the body, but these had not been associated with symptoms. He could not recall where they had appeared first but had noticed that they had increased progressively in number. In addition, in the last 12 years he had had painless swelling of the ankles. This was often considerable in the summer, extending up to the mid-calf, but in the winter the edema almost disappeared. Erect posture aggravated the swelling. For at least 13 years he had noted sensitivity of the hands to cold. His fingertips would blanch and feel numb after short exposure to cold, but there was no pain. They returned to normal in warm surroundings. In the summer such symptoms did not occur, but he then perspired extremely little and only in the axillae. In 1940, after more than usual exposure of his hands to cold he developed "blisters" all over the hands. These ultimately subsided and did not recur.

For an indefinite number of years he had had vague pain in the muscles, occasional cramps in the calves, and stiffness in the neck. There was no swelling of the joints. The pains were regarded as of rheumatic origin, and in 1945 all his teeth were extracted.

In 1951 he suffered from diarrhea of unknown etiology for three months. In December, 1951, he was hospitalized elsewhere for a short febrile episode. Chest x-rays, plasma proteins, and blood urea nitrogen were normal, and the blood pressure was only 100/70, but anemia was found. During 1952 he felt fairly well and worked regularly. Since January, 1953, he had suffered from lack of energy, occipital headaches, and occasional dizziness.

There had never been bleeding of any kind, shortness of breath, or loss of weight. He smokes 20 cigarettes daily but consumes no alcohol.

Family history: Both his parents are Norwegian. The father is alive and well at 67. His mother died of blood poisoning. No instance of any skin affliction was recalled by the patient on either the mother's or the father's side. Of the three living paternal aunts, one had been told by a physician that she was a bleeder. Four living sisters and two living brothers of the patient were all stated to be well, with no skin affliction. The family history was otherwise noncontributory.

Physical examination revealed a man of medium height, of fair complexion and somewhat sallow face, who seemed to be in good nutritional status. The pulse rate was 76 and regular. The blood pressure was 120/70.

Skin (Figs. 1, 2, 3, and 4): Over the thorax, especially posteriorly and laterally; around and on the umbilicus, and over the buttocks, pubis, scrotum, dorsum of the penis, the proximal parts of the extremities, and the patellar areas innumerable pinpoint- to pinhead-sized spots could be seen. Their color ranged from dark- to black-red. The smaller ones were flat; the larger ones, slightly raised. They tended to be grouped together in a rather symmetrical fashion. The largest ones were found on the genitalia and umbilicus; the tiniest ones, over the knees and the upper arms. The skin felt somewhat rough over the areas with the larger lesions. The face, the hands, and the lower extremities distal to the knees were entirely free of any such lesions. Some of the spots blanched on pressure with a fine point.

In addition to these lesions, on the palms and soles a number of indurated, dirty yellow lesions, measuring 1 to 2 mm. in diameter, were present. They resembled small corns.

Head: The frontal bosses and the lower jaw were prominent. There was slight puffiness of the eyelids, especially the lower lids. This was said to have been present always. The ocular movements were normal. On the inner canthi and the bulbar and palpebral conjunctivae aneurysmal dilatations of the vessels, pinpoint in size, could be seen. There were no opacities in the cornea. The pupils were equal, and the reflexes were normal. The optic discs

Fig. 4.—Scrotal lesions in Patient D. B. B.

were normal. There were no hemorrhages, exudates, or abnormal pigmentation in the retinae, and the vessels were normal except for a small aneurysmal dilatation visible along the course of a vein at the periphery of the lower left temporal quadrant.

The ears and nose were normal, without vascular abnormalities.

Mouth: Flat pinpoint purplish spots, arranged in linear fashion, were present in great numbers at the point of junction of the skin of the lip and the labial mucosa. These were more prominent on the upper lip, where they extended as far as the transition to the gingival mucosa. Fewer lesions were seen on the mucosa of the cheeks, and there were none on or underneath the tongue or on the palate.

The patient wore complete dentures. The throat was normal. The thyroid was not palpable. The lymph nodes were not remarkable in the neck or elsewhere.

The chest was symmetrical. No abnormalities were detected by percussion or auscultation.

The heart was not enlarged. The first sound was distinct and slightly snapping over the apex; no murmurs were heard.

Abdomen: The spleen and liver were not palpable. The right kidney could be palpated, but it was considered to be of normal size.

Genitalia: Except for the skin lesions over the praeputium, penis, and scrotum, no abnormalities were noted. Rectal examination and sigmoidoscopy were negative.

Extremities: Pulsations were normal throughout, and the temperature of the skin was normal to the touch. The joints were normal. The fingers were short and thick; the nails were curved, but there was no definite clubbing. The nailbeds were very white, out of proportion to the slight anemia. Slight, nontender nonpitting edema, which gave the sensation of rubber on pressure, was present over the dorsum of the feet and the ankles. The overlying skin was normal.

Neurological examination: No abnormalities were found.

Five months later (September, 1953) the swelling of the legs was more prominent, greater on the right than on the left, and pitted easily. No other changes in the physical findings were seen. There were no signs of phlebothrombosis. The pulsations of the dorsalis pedis could not be felt because of the edema. According to the patient's statement, the swelling had been worse that summer than ever before. It had extended up to the knees but regressed somewhat as the weather became cooler. He perspired very little and had had stiffness of the neck and of many joints, as in previous summers.

On the patient's third visit, in March, 1954, the swelling of the legs had decreased markedly and he was not suffering from joint stiffness. As always in the winter, the manifestations of sensitivity of the hands to cold were present. On examination no change in the patient's general appearance and skin lesions was seen, but, for the first time, three nontender movable subcutaneous nodules about 0.3 by 0.3 cm. were found on the inner aspect of the left elbow and a similar larger nodule (0.5 by 0.7 cm.) was felt on the posterior aspect of the right arm midway between the elbow and the axilla. These nodules might have been overlooked on previous examinations, since the patient stated that they had been present for two years. Only minimal edema of the ankles was present at this time, more on the right. The blood pressure was 112/80, and pulsations in the extremities were normal. Three months later, in June, the swelling of the legs had started once more to increase.

TABLE 1.—*Laboratory Findings in Patient D. B. B.*

	April, 1953	Sept., 1953	March, 1954	June, 1954
Volume of packed red cells, ml./100 ml.	42.5	41.5	40.5	41.5
Leucocytes/cu. mm.	7800	8500	10,150	....
Platelets/cu. mm.	272,000	190,000	....	....
Reticulocytes, %	1.8	....	....	....
Eosinophiles, %	7.5-10	10	5	9
Blood urea nitrogen, mg./100 ml.	13	14	11	10.5
Creatinine, mg./100 ml.	....	1.4	....	....
Phenolsulfonphthalein excretion, % in 15 min. and 120 min.	7/37	10/50	....	....
Serum albumin, gm./100 ml.	4.2	5.0	5.1	4.7
Serum globulin, gm./100 ml.	2.4	1.8	2.1	2.2
Calcium, mg./100 ml.	....	9.2	....	....
Phosphorus, mg./100 ml.	....	4.6	....	....
Cholesterol, mg./100 ml.	180	340	273	259
Plasma iron, γ/100 ml.	95	....	....	....
Plasma copper, γ/100 ml.	112	....	....	....
Basal metabolic rate, %	—11	—10, —6	....	....
Protein-bound iodine (normal 4-8 γ/100 ml.)	....	4.1	....	....
Liver-function Tests				
Sulfobromophthalein retention, 50 mg./kg., after 45 min.	0%	....	....	....
Thymol turbidity	3.5	....	....	....
Alkaline phosphatase (Bodansky units)	2.5	....	....	....
Cephalin flocculation	3+	....	....	....

The results of the various laboratory investigations done during the patient's four visits may be summarized as follows. Additional laboratory data are presented in Table 1.

Urine: constant low-grade proteineinuria (trace to 1+, once 2+), 0.61 gm./24 hr. by the biuret method (normal, 0.04 gm.); persistently low specific gravity, maximal concentration 1.010; no reducing substances; amino acid excretion, 236 mg. N/24

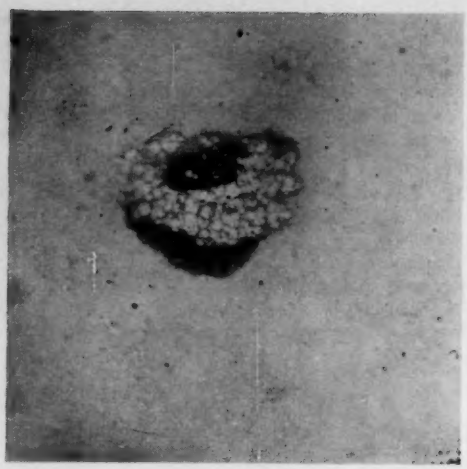


Fig. 5.—Vacuolated cell in urinary sediment; reduced slightly from mag. × 500.

hours (normal, 100 to 210 mg.). The sediment contained rare white and red cells and rare hyaline as well as some granular casts.

Large round or oval cells resembling macrophages and containing innumerable "lipoid" globules were constantly present in the sediment. In stained specimens one or two small, irregularly distorted nuclei could be seen in these cells and the cytoplasm displayed a foamy structure, the globules remaining unstained (Fig. 5). Free globules, single or in small groups, were seen in fresh sediment. Under polarized light doubly refractile globules having the characteristic appearance of "Maltese crosses" could be seen, intracellularly and free.

The red cell indices, erythrocyte sedimentation rate, and icterus index were normal. The blood smear was normal except for slight anisocytosis, poikilocytosis, and eosinophilia. The stools were negative for blood, ova, and parasites. Urine cultures were negative.

Tests for cryoglobulins and cold agglutinins were negative. The Kahn test was negative. The tourniquet test was also negative, and the bleeding and clotting times were normal.

Electrophoretic study of the serum proteins revealed a normal distribution of the various components.

Because of the suggestions which have been made that this form of angiokeratoma is actually a lipoid storage disease, certain serum measurements were made through the courtesy of Dr. J. Murray Steele, of New York. These are presented in Table 2. The total lipid phosphorus was somewhat low, but in other respects the findings were not abnormal.

An intravenous corticotropin (ACTH) test[27] produced a normal response of 17-hydroxycorticosteroid levels in the plasma.

The results of pulmonary and renal function tests are given in Table 3. The former were interpreted as compatible with some degree of emphysema or slight pulmonary fibrosis. Epinephrine injection influenced these results very little. The renal function tests revealed reduction of the glomerular filtration rate and decreased tubular reabsorptive capacity.

Sweating was tested by exposing the trunk and arms to heat and after injection of 10 mg. pilocarpine intramuscularly. There was little sweating in the axillae, less in the antecubital areas, and none in palms and trunk. Immersion of the hands in cold water (12 C) produced blanching of the fingers. The patient stated that they felt "dead,"

TABLE 3.—*Pulmonary and Renal Function Tests in Patient D. B. B.*

	Patient	Normal
I. Pulmonary function tests		
Vital capacity, ml.	3640	4600
Ventilation at rest, L./Min./m.^{2}	6.94	5-7
Maximal breathing capacity, L./min.	88.4	122
Maximal breathing capacity, following epinephrine	100	....
Arterial O_2 saturation, %	84	>90
II. Renal function tests		
Inulin clearance (glomerular filtration rate), ml./min.	64.5	130 ± 20
p-Aminohippurate (PAH) clearance (renal plasma flow), ml./min.	428	700 ± 130
Tm PAH (tubular excretory capacity), mg./min.	70.5	76
Tm glucose (tubular reabsorptive capacity), mg./min.	200	375 ± 80

TABLE 2.—*Serum Lipids in Patient D. B. B.**

		Total Cholesterol, Mg./100 Ml.	Total Lipid Phosphorus, Micromoles/L.	Lecithin Phosphorus, Micromoles/L.	Sphyngomyelin Phosphorus, Micromoles/L.	Lecithin/ Sphyngomyelin, Micromoles/L.
Whole serum		218.0 (190-250)	2.22 (2.5-3.5)	1.90 (2.0-3.0)	0.44 (0.3-0.5)	....
Lipoproteins	α	43.5 (30-60)	0.74 (0.8-1.2)	0.70 (0.3-0.9)	0.07 (0.05-0.12)	10.0 (6-18)
	β	175.0 (120-190)	1.45 (1.2-2.8)	1.18 (0.4-1.3)	0.36 (0.10-0.40)	3.3 (2-3.5)

* Normal values are shown in parentheses.

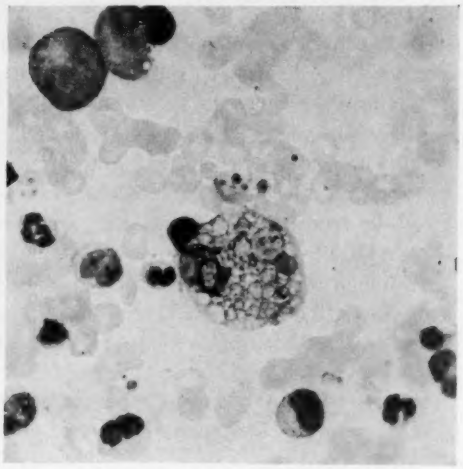


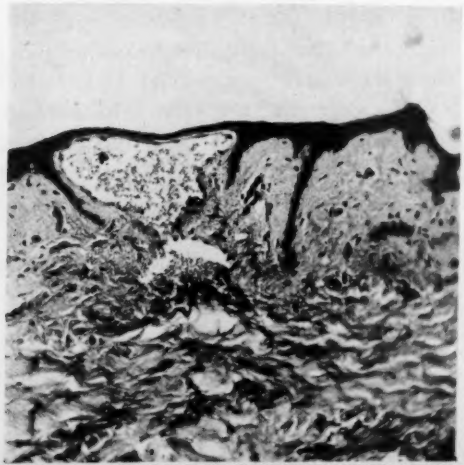
Fig. 6.—Vacuolated macrophage in bone marrow aspirate; reduced slightly from mag. × 500.

and, indeed, pronounced hypasthesia to painful stimuli was present. Five minutes after withdrawal the fingers became normal, without the development of pain, flushing, or cyanosis. The blanching was even more striking after exposure for seven minutes in a cold room (4 C) and was accompanied by a chill. Only after 25 minutes at room temperature did his hands return to normal.

Initial roentgenographic studies of the chest, abdomen, and kidneys were normal. A film of the skull showed a sella turcica at the upper limits of normal in size, poorly developed paranasal sinuses, and prominent frontal bosses. Fourteen months later no change was seen in the skull, but the heart had obviously increased in size.

Electrocardiograms on two occasions indicated questionable left ventricular hypertrophy and showed an abnormally short PR interval (0.11 and 0.12, with rates of 75 and 65, respectively). The electrocardiogram showed no further changes with the anoxia test.

Fig. 7.—Subepidermal vascular aneurysm from skin of the lumbar area; hematoxylin and eosin; reduced slightly from mag. × 200.



The following biopsies were performed:

Bone marrow (sternal aspiration): normal, except for a very rare heavily vacuolated large "foamy" macrophage (Fig. 6).

Skin (from lumbar area): immediately under the basal layer of the epidermis, irregular microscopic vascular spaces were found, partially filled with blood. There was no hyperkeratosis (Fig. 7).

Corn-like lesion from the ulnar border of the palm: marked hyperkeratosis and thickened epidermis. The dermis consisted chiefly of dense collagen fibers containing normal skin appendages. The blood vessels were not remarkable.

Section of a 0.5 by 1 cm. subcutaneous nodule from the right upper arm showed a portion of skin with subcutaneous fat which was so vascular that it resembled an angioma spread apart by lipoid vacuoles (Fig. 8). Basophilic material seen in some of the vacuoles was not metachromatic nor did it stain with the periodic acid technique. Therefore, it was probably not a polysaccharide. Fat stains revealed no abnormal fat deposits. Collagen fibers were the only doubly refractile material seen.

Inguinal lymph node: extensive fibrosis. The capsule was thick and fibrous. The subcapsular sinus contained dense accumulations of lymphocytes and occasional foci of macrophages. Areas of reticulum hyperplasia were prominent.

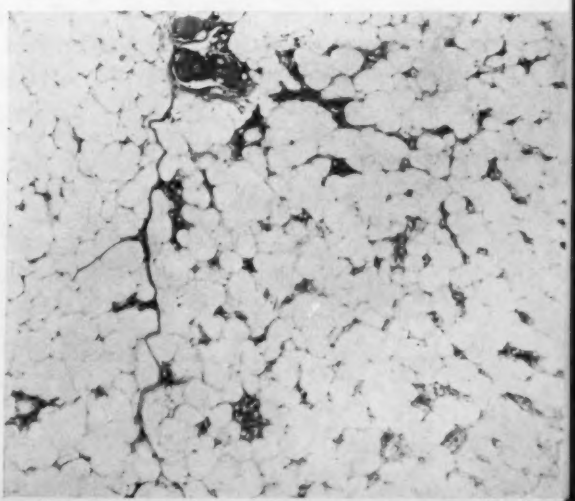
Striated muscle (left gastrocnemius): unremarkable. There were no abnormalities in either muscle or blood vessels.

Frozen sections of the skin, muscle, and lymph node, stained with Sudan IV, failed to show intracellular fat. Examination of frozen sections with polarized light failed to reveal doubly refractile bodies.

Liver (needle biopsy): Normal architecture. No evidence of lipoid.

Two sisters, one brother, and the son of the patient's sister were examined and were found to have no symptoms or physical or urinary findings similar to those of our patient.

Fig. 8.—Subcutaneous fat with excessive numbers of small capillaries filled with red blood cells; hematoxylin and eosin; × 200.



COMMENT

We have attempted to review the published literature on angiokeratoma corporis diffusum universale (Fabry) and have included all cases described under this or other names which fit, in one way or another, the picture of the disorder. From the information given in the published reports, the cases tend to fall into two groups (Table 4), as follows:

Group I. Cases presenting the dermatological features of the disease, with evidence of systemic involvement or findings suggestive of it, such as those of Fabry,¶ Anderson,[6] Steiner and Voerner,[7] Sibley,[10] Weicksel,[11] Ruiter and co-workers,# Hornbostel and co-workers,* and Brown and Milne.[26] Our case appears to fit into this category. The cases of Head,[28] Netherton,[29] and Woehnlich,[30] although not recognized as examples of angiokeratoma and though presenting some atypical features, probably also belong here.

Group II. Cases characterized by the dermatological features but without information concerning the presence or absence of systemic manifestations, possibly because of the incompleteness of the published data: Stümpke[9] and Volavsek.[16] The cases of Madden[31] and probably those of Fuhs[32] and Bechet[33] also belong in this group.

In agreement with Hornbostel and coworkers[23] we have excluded the case of Taguchi.[14] We have also excluded that of Robba,[13] because of a very different distribution of the skin lesions, even though signs of chronic nephritis were present. The cases of Parisi[34] and Halter[35] have been excluded, with some hesitation and in spite of many similarities, because of the late and sudden appearance of the skin lesions at 26 and 30 years of age, respectively. Too little information was available concerning the cases of Rille,† Martenstein,[12] and Tuma and Halacka[15] to permit their inclusion in the present survey.

From a study of the cases hitherto described as well as on the basis of our own observations, the following clinical picture of this rare disorder may be outlined.

The condition has been described so far mainly in persons of North European extraction and only in males. No clear example of the syndrome, not even the typical skin manifestations, has been reported in a female.

Although the disorder has been described in brothers, the hereditary nature of the condition has not been proved conclusively. In no instance was one of the parents or offspring affected by a similar skin condition. Consanguinity of the parents has never been mentioned.

The earliest manifestations of the disease are the minute "red spots" on the skin, which first appear in childhood or adolescence and become more numerous as time goes on. Their progression sometimes ceases in later life. At first they are restricted to the lower part of the trunk or the upper part of the lower extremities. Other areas become affected later to varying degrees. The lesions generally have a centripetal distribution, occur in groups, and are dense and larger on the lower trunk (scrotum, penis, buttocks, lower back, upper thighs, umbilicus) and more sparse on the upper parts of the trunk and upper extremities. Lesions have been found on the lips and the buccal mucosa in many cases but are unusual elsewhere on the face. Involvement of the palms and soles is uncommon but has been observed. The skin over the affected areas is rough. The larger lesions may be raised; the small ones are flat. They do not have a tendency to bleed. Some can be blanched by pressure with a fine point. Their color ranges from dark-red to bluish-red. The skin is otherwise normal.

On the bulbar and palpebral conjunctivae, along the venules, aneurysmal dilatations of varying degree may be seen. In addition, increased tortuosity of the retinal vessels, with aneurysmal dilatations along their course, may be observed. In some cases, peculiar peripheral inconspicuous corneal opacities have been described. In spite of these

¶ References 2-4.

References 17 and 18.

* References 20-25.

† Rille: Angiokeratosis universalis, cited by Fabry.[4]

TABLE 4.—*Summary of Findings in Reported Cases and Present Case* *

	Group I															Group II							
	Fabry [2-4]	Anderson [6]	Steiner and Voerner [7]	Sibley [10]	Weicksel [11]		Eulter, Pompen, and Wyers [17-19]				Hornbostel and Others [20-25]		Present Case	Brown and Milne [26]		Head [28]	Netherton [29]	Wöhnlich [30]	Strümpke [9]	Fuhs [32]	Madden [31]	Volavsek [14]	Bechet [33]
Origin	German	English	German	English	German		Dutch				German		Norwegian	Scotch		Swedish	?	German	German	?	?	?	?
Sex	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Age at first examination,† yr	13 (42)	39	28	21	22 (Brothers)	18	32 (39)	28 (Brothers)	27	(46)	(46)	50	35	30 (Half-Brothers)	29	28	25	32	28	26	33	26	30
Siblings affected	..	..	..	Male?	..	..	..	..	..	..	Male?	..	..	..	..	..	..	..	2 Male	..	..	..	..
Age of onset (skin lesions)	9	11	18	15	10	10	Childhood			10	Youth	12	Childhood	7	13	14	14	14	14	16	12	Childhood	16
Skin lesions (typical distribution and appearance)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosal lesions	+	..	+	+	+	+	−	−	−	−	+	+	+	+	+	−	..	+	..	..	+	..	−
Eye lesions																							
(*a*) conjunctivae	..	..	..	..	+	+	..	..	..	..	+	+	+	..	..	..	+	+	..	..	+	..	..
(*b*) corneal opacities	..	..	..	..	+	+	..	+‡	+‡	..	..	..	−	..	..	..	..	..	..	..	..	..	..
(*c*) fundi (vascular)	..	..	+	..	+	+	+?	..	..	+?	+	+	±	..	..	..	+	+	..	..	..	..	..
Edema of legs	..	..	..	..	..	..	+	+	+	+	+	..	+	..	..	..	..	+	..	..	..	..	..
Diminished sweating	..	..	+	..	..	..	+	+	..	+	..	..	+	..	..	+	..	..	..	..	..	..	..
Sensitivity to cold	..	..	+	..	..	..	+	+	..	+	+	..	+	..	..	..	..	+?	..	..	..	..	..
Sensitivity to heat	..	..	+	..	..	..	+	+	+	..	..	..	+	..	..	..	+	..	..	..	..	..	..
Rheumatoid pains, cramps, paresthesias	..	..	+	+	..	..	−	+	+	+	+	..	+	+	+	+	+	..	+	..	..	..	..
Urinary abnormalities																							
(*a*) proteinuria	+‡	+	+	+	−	−	+	+	+	+	+	+	+	−	−	+	..	..	−	..	..	..	..
(*b*) low specific gravity	..	..	..	+	..	..	+	+	+	+	+	+	+	−	−	..	..	..	..	..	..	..	..
(*c*) WBC, RBC, casts	..	..	+	+§	..	..	+	+	+	+	+	+	+§	−	−	..	..	..	..	..	..	..	..
Cardiomegaly (clinical or by x-ray)	..	..	..	..	..	+	+	+	+	+	+	+	+	..	..	..	..	..	..	..	..	..	..
Emphysema	+‡	..	..	..	..	..	+?	..	..	..	+	+	+	..	..	..	..	..	..	..	..	..	..
Blood pressure	..	..	..	Loud A_2	..	..	180/130	170/100	135/75	160/110	130/75	..	120/70	..	..	..	..	Very low	..	..	..	..	..

* The signs + or − indicate that a definite statement is made regarding the findings. No attempt is made to quantitate the findings. Absence of these signs signifies that neither negative nor positive findings are mentioned.

† Age at death is given in parentheses.

‡ Findings at a later examination.

§ Lipoiduria.

changes, the patients' vision appears to have been unimpaired.

A second group of symptoms and signs which become noticeable to the patient relatively early in the course of the disease are rheumatoid pains, cramps, and paresthesias in the extremities. The patients may exhibit sensitivity to cold or to heat or both. Blue or blanched hands, "dead" fingers, and flushing of the extremities are common. The patients seem to have difficulty in adjusting themselves to temperature changes. Diminished sweating is noted in many patients but not in all.

Swelling of the legs of varying degree is also a common feature of the disease and had been present for many years in almost all the cases studied in some detail. The marked seasonal variation of the swelling noted in our patient has not been mentioned in any of the cases reported hitherto.

The above symptoms may be present for years without rapid aggravation or change. Usually in the third or fourth decade inconstant vague complaints of mental or physical weakness, headaches, and dizziness make their appearance. Of the more definite signs appearing in later life, shortness of breath is prominent. Urinary complaints are unusual.

In addition to the dermal, mucosal, and ocular changes; the edema of the extremities, and the symptoms which have been discussed above, certain other features deserve mention.

An elevated blood pressure, affecting both the systolic and the diastolic pressures, was present in three of the six cases for which data were given. Cardiomegaly, demonstrable clinically or roentgenographically, mainly leftsided, was observed in all of seven well-studied cases, and the electrocardiogram was indicative of diffuse myocardial damage. Cardiac insufficiency was present in two of the cases.

Emphysema demonstrable clinically or by pulmonary studies was present in three cases (in a fourth changes in the lungs were present at autopsy).

A renal syndrome was present in some degree in most of the cases which were adequately studied: proteinuria, low specific gravity or isosthenuria, microscopic hematuria, and cylindruria. Our patient also exhibited lipoiduria. The renal syndrome may be present for many years before health is seriously impaired. The blood urea nitrogen was elevated in the advanced cases.

Enlargement of the liver has been noted only in patients in cardiac failure. Significant lymphadenopathy has not been seen in any of the typical cases, but splenic enlargement was observed in one of the patients of Brown and Milne [26] and in Woehnlich's case.[30] The latter presented hepatosplenomegaly and thrombocytopenia. Unfortunately, the study was not complete and no autopsy was performed.

Neurological involvement has not been demonstrated clinically, with one exception.[26]

Blood chemical examinations so far have failed to reveal any clear abnormality in protein or lipid metabolism.

Slight to moderate anemia was present in several cases, and definite eosinophilia was found in two of the six cases in which a differential leucocyte count was reported. No other abnormalities have been noted in the blood.

Death occurred from uremia in two cases and probably from a myocardial infarction in the third (at the ages of 39, 46, and 46 years, respectively). Another patient was alive at 50, however, in spite of obvious renal, cardiac, and pulmonary involvement.

The pathological findings common to the three autopsied cases and the single biopsied case indicate the presence mainly of some abnormality in the smooth muscle of the entire vascular system: considerable increase in the size of the media and a varying degree of vacuolization of the smooth muscle cells by a substance which was found in two cases to be birefringent under polarized light. This substance was not stainable by Sudan III [18] and could be stained only faintly by hematoxylin and Sudan IV.[21] Some of the nuclei appeared bizarre and polymorphous. Pronounced central vacuolization of the muscle fibers could also be seen in the cardiac muscle. The vacuoles showed birefringence. Car-

diac hypertrophy, present in all the autopsied cases, was definitely right-sided in one of them. Two of these patients were hypertensive.

The vascular changes have been described in almost all the organs but have been most pronounced in the kidneys. Here, thickening of the intima has been observed also, especially in the smaller arteries, as well as storage of doubly refractile material in Bowman's capsule and in the tubular epithelial cells. Glomerular changes difficult of interpretation were seen in one case.[18]

In our case vascular changes were demonstrable in some of the vessels of the skin and in the lymph node biopsy, these consisting of slight thickening and vacuolation of the media. No doubly refractile or stainable lipid substances could be demonstrated in the sections examined. Our failure might be explained by insufficiency of material for study or examination at too early a stage of the disease. On the other hand, we found free and intracellular birefringent bodies in the urinary sediment repeatedly.

"Foam" cells have been seen in lymph nodes, spleen, and adrenals, and vacuolation of varying degree due to lipoid material has been demonstrated in the Kupffer cells of the liver, in the reticulum cells of the lymph nodes and spleen, and in the ganglionic cells in several areas in the central and peripheral nervous system. This material also showed birefringence under polarized light.[21] We were able to demonstrate "foam" cells in bone marrow aspirates, in the lymph node biopsy, and in the urinary sediment. The spleen contained increased amounts of iron-containing pigment in the two cases in which the specific stain was mentioned.

The lungs, reported in two cases,[18] were definitely abnormal in only one, showing, in addition to the omnipresent vascular lesions, vacuolization of the bronchial epithelium and a peculiar precipitate in or on the alveolar walls. Its nature could not be ascertained by the various staining methods which were used.

The skin lesions are generally described as consisting of vascular spaces of varying size, lying in the papillae, filled with blood or thrombi, and lined by a single layer of endothelium. The epidermis may be thin over these lesions. Hyperkeratosis is not a constant finding. Similar angiectases were seen in the mucosa of the gastrointestinal tract, the trachea, and the renal pelvis in only one case.[20] Vascular changes of the pattern already described have also been seen in the deeper layers of the skin.

An increased amount of glycogen has been observed in the liver, the striated muscle, the cardiac muscle, and the smooth muscle of the vessels; however, no quantitative analysis has been done.[21]

Chemical analysis of the cardiac muscle in one case showed a 10-fold increase of the diaminophosphatides. These differed from the sphingomyelins in solubility (Kühnau, Hamburg, cited by Scriba[21]).

Little can be said concerning the nature of this syndrome. Ruiter and co-workers ‡ suggested that this is a storage disease. Because of the optical characteristics of the stored substance in two cases and chemical analysis in one, Scriba [21] concluded that the stored material is a lipoid. So far, no abnormal constituent of the serum lipids has been reported. More complete studies are necessary, however. The differences between this disorder and other known lipoid storage diseases are evident on clinical as well as pathological grounds (e. g., absence of hepatosplenomegaly, different staining characteristics, different localization of the storage phenomena).

The connection between the skin and the mucosal telangiectases and the abnormality of the larger vessels is not clear. Similarly, the peripheral edema and the symptoms in the extremities remain unexplained. There is a better anatomical basis for the renal, cardiac, and pulmonary symptomatology.

The cause of the diminished sweating also remains obscure. An anatomical basis for this has not been adequately investigated.

‡ References 17-19.

From the evidence presented, one has to assume that the error in lipid metabolism, if one exists, affects the smooth muscle. However, while changes have been seen consistently in the heart and vascular muscle, no data have been presented regarding the morphology of the visceral muscles. The muscle cells of the arrectores pili were found to be normal in one case [18] but presented some vacuolization in our case. Changes in the striated muscle similar to those of the smooth muscle fibers were seen in only one autopsy.[21] It should be pointed out, however, that not all the cases have been examined by the same methods.

Additional problems of significance are (*a*) the possible hereditary nature of the disease. For the present a recessive sex-linked inheritance can be assumed only as a working hypothesis; (*b*) the possibility that the syndrome may present itself in incomplete form. The various cases which have been reported have not all had the same signs and symptoms nor did the disorder develop to the same degree; greater differences may be expected as more cases are studied.

From the standpoint of differential diagnosis it should be pointed out that several other types of angiokeratoma must be distinguished from the form under discussion. Angiokeratoma Mibelli is found usually on the bony protuberances of the extremities and is associated with exposure to cold and chilblains. These lesions are rough, hard, and warty and bleed freely when pricked with a needle. Angiokeratoma scroti (Fordyce) is localized to the scrotum and is found in elderly persons. Angiokeratoma naeviforme circumscriptum is localized to one area of the body and is usually unilateral.

More likely is the possibility of mistaking the lesions of angiokeratoma for those of purpura, as in fact they have been on a number of occasions, or those of multiple hereditary telangiectasia. Close examination reveals certain significant differences. The lesions of angiokeratoma corporis diffusum universale (Fabry) are mainly centripetal in distribution and are found principally on the trunk, especially the lower part, and on the proximal portions of the extremities. Their location about the umbilicus (Fig. 2) is rather unique. The lesions of hereditary telangiectasia are centrifugal in distribution and involve the face and the distal parts of the extremities. Like telangiectases and unlike the lesions of purpura, the lesions of angiokeratoma are more or less permanent. Although some of the lesions can be partially blanched on pressure, this is unusual and is in no way comparable to the blanching on pressure characteristic of telangiectases. Their color differs, moreover, being darker red than that of telangiectases and not purple as in purpura. Finally, there may be associated skin and subcutaneous manifestations such as the small corn-like lesions found on the palms and soles of our patient and the subcutaneous nodules in his arms, as well as swelling of the lower extremities and a number of complaints referable to the extremities.

SUMMARY

A case of angiokeratoma corporis diffusum universale (Fabry) presenting evidence of associated vascular, renal, cardiac, and pulmonary dysfunction is presented. This appears to be the first case studied in America.

The literature on the subject has been reviewed with the view, particularly, of seeking evidence concerning the systemic nature of the condition.

From the cases reported so far it can be said that angiokeratoma corporis diffusum universale (Fabry) constitutes a well-defined clinical entity, which involves many tissues in addition to the skin.

ADDENDUM

In an article published since the present paper was sent to press, Ruiter (Ruiter, M.: Histological Investigation of the Skin in Angiokeratoma Corporis Diffusum, in Particular with Regard to the Associated Disturbance of Phosphatid Metabolism, *Dermatologica* **109**:273, 1954) has reported the death, at age 47, of the second of his three cases [17] and described the deposition of a lipid substance in all the vessels of the skin, even the capillaries.

Dr. R. F. Miller, of Chester, Mont., referred Patient D. B. B.; Dr. J. Murray Steele, of New York University, made the determinations presented in Table 2, and Drs. R. H. Follis, O.

Rambo, and E. J. Eichwald, of the Department of Pathology, as well as a number of our colleagues in the Departments of Surgery, Biochemistry, and Medicine, of the University of Utah, assisted in this study.

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Treatment in Internal Medicine

TREATMENT OF MACROCYTIC ANEMIAS

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ANEMIAS characterized by large erythrocytes (MCV > 95) are usually caused by lack of one of the erythrocyte maturation factors, vitamin B_{12} or folinic acid. Under these circumstances the young erythrocytes in the bone marrow are megaloblastic and maturation of myeloid elements and megakaryocytes is bizarre. This discussion will be concerned primarily with these anemias (MCV up to 150). There are, however, other causes of macrocytic anemia which deserve mention. These are chronic liver disease, hypothyroidism, and hemolytic and aregenerative anemias. Under these conditions, the size of the erythrocyte is increased only moderately (MCV of 95 to 110) and the bone marrow is normoblastic rather than megaloblastic. These macrocytic anemias are in no way related to the erythrocyte maturation factor deficiency anemias, either etiologically or therapeutically, though the occurrence of large erythrocytes justifies including them in the classification of macrocytic anemias. They will be discussed as a separate group.

Selection of proper therapy depends upon correct diagnosis. Successful treatment has been evolved by careful observation, empirical trial, and gradual accumulation of data on the pathogenesis of the various types of macrocytic anemia. In order that one may appreciate the rationale of various therapeutic procedures, a brief discussion of pathologic physiology is essential.

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MACROCYTIC MEGALOBLASTIC ANEMIAS

This group includes pernicious anemia, nutritional macrocytic anemia, tropical macrocytic anemia, sprue, pernicious anemia of pregnancy, vitamin-B_{12}-refractory megaloblastic anemia (achrestic anemia), and the megaloblastic anemias of infancy, of scurvy, of gastrointestinal tract anomalies, of the total gastrectomy syndrome, of fish tapeworm infestation, and of completely unknown etiology. In each of these anemias, the peripheral blood and bone marrow have the same characteristics: macrocytosis, extreme variation in the size and shape of the erythrocytes, leucopenia, multilobed aged polymorphonuclear leucocytes, and thrombopenia. These characteristics are the result of maturation arrest of the erythroid, myeloid, and megakaryocytic elements of the bone marrow. Each occurs, in all probability, because of abnormalities in the intracellular chemical chain reaction necessary for the formation of the nucleic acids.

By this reaction, carbon and hydrogen from simple compounds such as aminoacetic acid (glycine) and formate; nitrogen from the nitrogen pool of the body, particularly glutamine and glutamic acid, and phosphorus from high-energy phosphate are built into complex nucleotides. The nucleic acids are formed from these compounds after conjugation and polymerization. Purine and pyrimidine bases are way stations along the course of this reaction. One bit of evidence linking abnormalities in this reaction to the megaloblastic anemias is the hematologic improvement that can be attained in patients with pernicious anemia treated with large doses of thymine and uracil, two pyrimidine bases.

Certain steps in this reaction are catalyzed by enzyme systems of which folic acid and

vitamin B_{12} are important parts. The reader is referred to several recent reviews from the voluminous literature that has been published on this subject.* Recent evidence suggests that folic and folinic acid conjugates from food are converted in the body successively to folic acid, folinic acid, and folinic acid coenzyme by tissue conjugases, ascorbic acid, other reducing substances, and a complex adenosinetriphosphate-dependent enzyme system. Folinic acid coenzyme is essential for the transfer of single carbon units, and in this role it is involved in the synthesis of the complex purine ring structure and in the methylation of uracil ribotide to the thymine deoxyribotides. Lactobacillus casei and Streptococcus faecalis will use thymine or thymidine and Leuconostoc citrovorum will use thymidine for growth in place of folic and folinic acids, respectively.

Vitamin B_{12} also is involved in the transfer of single carbon units, probably in a less direct fashion than is folinic acid. This vitamin is essential for certain reduction systems and for the activation of enzymes containing sulfhydryl groups (SH-). It may be involved indirectly in the formation of folinic coenzyme, thus adding to the complexities of the relationships between folinic acid and vitamin B_{12}. It can be replaced by thymidine as a necessary growth-promoting substance for Lactobacillus leischmannii and S. faecalis. Therefore both the complex folic acid-ascorbic acid system and vitamin B_{12} are necessary for the formation of the nucleic acids, particularly of the nuclear deoxyribose-thymine-containing type. Without a sufficient supply of this essential nuclear material, division of cells is slowed, but protein formation continues, controlled by cytoplasmic and nucleolar ribose nucleic acid (the material in cytoplasm and nucleoli stained blue in Wright-Giemsa stain). Apparently ribose nucleic acid formation is less disorganized than that of deoxyribonucleic acid by deficiencies of these substances. The cells grow, but they divide only infrequently. When erythrocytes develop in this fashion, the result is the large megaloblast in the bone marrow and the macrocyte in the peripheral blood. So far, only deficiencies of one or more parts of this system are known to produce macrocytic megaloblastic anemia, and by the same token only anemias which occur because of such deficiencies will respond to these erythrocyte maturation factors. In some instances, the anomalies which bring about these deficiencies also envoke distinctive clinical features which aid in diagnosis. In other instances, this does not happen and only a carefully controlled therapeutic trial will establish the correct diagnosis.

ANEMIAS DUE TO CONDITIONED DEFICIENCIES OF VITAMIN B_{12}

Pernicious anemia, the commonest of this group, occurs because of a gastric defect of unknown cause, a lack of intrinsic factor. This factor, a protein enzyme which only recently has become available in sufficient amounts for commercial use, is necessary for the proper absorption of vitamin B_{12} from food, either by protecting it from destructive forces in the intestine or by facilitating its passage through the intestinal wall.[5] A deficiency of this substance results, in time, in a cellular deficiency of vitamin B_{12}. Such a defect impairs not only the production of blood in the bone marrow, by processes just described, but also reduces very significantly the life span of the cells produced,[6] interferes in some unknown way with bile pigment metabolism,[7] and alters the form and function of the cells of mucous membranes,[8] the central and peripheral nervous systems,† and, probably to a lesser extent, all other cells of the body. The result is hemolytic jaundice, irreversable achlorhydria and achylia, glossitis, gastritis, peripheral neuritis, and posterolateral column degeneration.

On the strength of the belief that pernicious anemia was a deficiency disease and Whipple's evidence that liver was helpful for the regeneration of blood in anemic dogs, Minot and Murphy fed liver to patients with pernicious anemia.[11] Following the dramatic

* References 1-4.

† References 9 and 10.

success of this therapy, liver extracts were made for parenteral use. These were refined and concentrated, but only recently the active principal in these extracts has been found to be vitamin B_{12}.‡ The substance which was effective in the oral liver preparations must have been folinic acid. Since we know that folic or folinic acids are incomplete therapy for pernicious anemia patients, our most important therapeutic tools are vitamin B_{12} or refined liver extract given parenterally, to circumvent the gastric defect and restore nucleic acid metabolism to normal.

Macrocytic megaloblastic anemia analogous to pernicious anemia may occur in persons infested with the fish tapeworm, Diphylobothrium latum. Most of the information on this subject comes from the Scandinavian countries, where such infestations are commonest. The worm, or products of its metabolism, interferes with the action of the intrinsic factor, which promotes the absorption of vitamin B_{12} through the intestinal wall.[14] Therefore, the clinical and hematological syndrome that results is quite the same as in pernicious anemia. Parenteral vitamin B_{12} or refined liver extract will induce a satisfactory hematological response, but removal of the worm is the procedure of choice, since by this means the entire pathological process is reversed.

Many years after total gastrectomy, megaloblastic anemia equivalent to pernicious anemia may appear. The cause is the surgical removal of the fundal portion of the stomach which secretes the intrinsic factor. In this fashion pernicious anemia is produced artificially, absorption of vitamin B_{12} is reduced to very small amounts, and the only reason the syndrome appears after a long latent period is the capacity of the body to hold tenaciously to its vitamin B_{12} stores.§

Another way by which the cells of the body may be deprived of vitamin B_{12} is through a deficiency of the vitamin-B_{12}-binding proteins of the plasma. These proteins, which are found in the alpha 1 and alpha 2 globulins, carry the vitamin in bound form from the intestine to the cells. Bound vitamin B_{12} tends to be retained in the body. The unbound vitamin is rapidly excreted in the urine. It is theoretically possible that a syndrome analogous to pernicious anemia, except for the gastric defect, might occur if, for some reason, there was a deficiency of these binding proteins. Such a situation has been reported by Horrigan and Heinle.[18] Their patient failed to respond to vitamin B_{12} or folic acid and excreted most of a test dose of vitamin B_{12} tagged with radioactive cobalt administered parenterally. A hematologic response occurred when the vitamin was given with a transfusion of normal plasma, presumably containing the binding proteins. This would seem to be the logical treatment for this extremely rare condition.

ANEMIAS DUE TO DIETARY DEFICIENCIES OF VITAMIN B_{12} AND/OR THE FOLINIC ACID-ASCORBIC ACID GROUP

Nutritional macrocytic anemia is due to prolonged dietary inadequacy in one or more of the erythrocyte maturation factors. A diet deficient in animal protein—and therefore in vitamin B_{12}—is the usual cause,[19] though deficiencies in the folic acid-ascorbic acid system may play a more or less important role. In some patients it may be the primary deficiency. This type of anemia occurs most frequently in persons with other vitamin-B-complex-deficiency diseases, such as pellagra or beriberi. Though the origin is probably a dietary deficiency in vitamin B_{12} and/or folic acid, defects in gastroenteric tract absorption follow and additional deficiencies of erythrocyte maturation factors are induced. Therefore, whether or not the patient's diet was grossly deficient in folic acid, a lack of this substance ultimately occurs and accentuates the anemia. The chemical interrelationships of vitamin B_{12} to folic acid metabolism may lead to a conditioned deficiency of folinic acid also.

In contrast to persons with pernicious anemia, these patients usually have nonfatty diarrhea and are not jaundiced; they may or may not have free hydrochloric acid in their

‡ References 12 and 13.

§ References 15-17.

gastric secretions while anemic, but they usually recover this gastric function after treatment; they seldom have more extensive nervous system involvement than peripheral neuritis, and, after definitive treatment, they remain well as long as they eat an adequate diet with emphasis on animal protein. On the basis of what has been learned regarding the biochemistry of these factors it is not clear why, in this counterpart of pernicious anemia, the cord should be spared and hemolytic jaundice should be rare. Several theories have been suggested, but nothing has been proved. The reversibility of the gastric lesion and the response to dietary improvement are expected in the light of etiologic mechanisms.

Vitamin B_{12} by the oral route (extrinsic factor of Castle) will usually induce a hematologic response unless the absorptive functions of the gastrointestinal tract have been too badly impaired by long illness. Under these circumstances, parenteral vitamin B_{12} is indicated. Oral folic acid is equally efficacious, but under any circumstances the diet must be improved, especially in regard to animal protein.

The exact etiology of sprue is still in doubt, though the most compelling evidence favors the theory of dietary deficiency in folic acid. A similar syndrome can be induced in monkeys by such a deficiency state.[20] The most important clinical feature of the sprue syndrome is steatorrhea with or without diarrhea due to serious impairment in the absorptive powers of the gastroenteric tract. This leads to multiple deficiency states, including those of vitamin B_{12} and ascorbic acid. The intrinsic factor content of the gastric juice of a patient with sprue is greatly reduced, but this also is a secondary phenomenon, and intrinsic factor given orally does not usually potentiate the absorption of vitamin B_{12} in such patients.[21] Except for the steatorrhea, there is little clinical difference between sprue and nutritional macrocytic anemia.

Folic acid by the oral route is the drug of choice, though good clinical responses may be obtained by treatment with vitamin B_{12} given parenterally in doses somewhat larger than necessary for the adequate treatment of pernicious anemia.

TROPICAL MACROCYTIC ANEMIA

In tropical regions, nutritional anemia with megaloblastic bone marrow is quite common. The majority of these patients are pregnant women. It is probable that the defect in folic acid metabolism which is discussed below under the title of pernicious anemia of pregnancy accentuates the dietary deficiencies of these women. It is likely also that these are mixed deficiency states and that they have varied etiologies depending on the diet of different tropical regions and the parasites that inhabit the intestinal tract of these patients. The patients studied by Lucy Wills [22] apparently were deficient in folic acid or an unknown factor related to folic acid metabolism (Will's factor). Whether such a factor exists is still open to question. It is clear that these patients were not deficient in the liver factor (vitamin B_{12}) alone, since a therapeutic response did not occur when they were treated with refined liver extract. They did improve when given a crude liver extract, which probably contained folic or folinic acids.

Recent reports || indicate that the majority of patients with tropical macrocytic anemia will respond to vitamin B_{12} in doses somewhat larger (4γ daily) than are required in pernicious anemia (1γ daily). The few that fail to respond to vitamin B_{12} will respond to folic acid. There is no data as yet concerning the effect of maintenance therapy.

Other diseases which impair the absorptive powers of the small bowel may result in a syndrome simulating sprue. In most cases the etiologies are unknown and the syndrome is referred to as idiopathic steatorrhea or nontropical sprue.[25] In others, such etiologic factors as regional ileitis, tuberculous enteritis, chronic idiopathic ulcerative colitis, or lipophagic granulomatosis may be the cause. The result of the intestinal defect is

|| References 23 and 24.

mixed deficiency disease, including a severe lack of folic acid and vitamin B_{12}. These deficiencies, particularly the former, intensify the absorptive error and cause the macrocytic megaloblastic anemia which usually, but not always, is associated with these syndromes. In other respects, also, the clinical features simulate sprue. Treatment with folic acid orally or vitamin B_{12} parenterally, as in sprue, will usually rectify the anemia and will overcome the absorptive defect caused by deficiency of these substances. Such therapy has no effect on the basic pathologic process in the intestine, which initiated the syndrome. Therefore, varying degrees of therapeutic response may be expected, depending upon the intensity of this basic pathology.

Other conditions involving the gastroenteric tract may cause macrocytic megaloblastic anemia also. These are exemplified by short circuiting operations which leave behind blind loops or blind pouches of intestine or conditions causing gastrocolic fistulae.[26] Exactly how these conditions cause macrocytic anemia is not known, though the basic abnormality is probably a change in the gastroenteric tract micro-organism. Perhaps such a change results in the production and availability of less folinic acid. Perhaps a metabolic antagonist for folinic acid or vitamin B_{12} is formed in the malfunctioning bowel, or perhaps the erythropoietic vitamins from the food are held by the gastrointestinal organisms and the absorption into the body prevented. Whichever of these or other theories may be correct, a sprue-like syndrome results, and, as in sprue, vitamin B_{12} is poorly absorbed, though plenty of intrinsic factor may be available. Folic acid, given orally, will usually rectify the defect in blood formation. Occasionally posterolateral column degeneration occurs, suggesting the need for parenteral therapy with vitamin B_{12}. Permanent improvement can be attained only by surgical repair of the gastroenteric anomaly.

Insufficiency of the exocrine functions of the pancreas, causing steatorrhea, may sometimes lead to macrocytic megaloblastic anemia by preventing the absorption of folic acid and vitamin B_{12}. These vitamins, particularly folic acid, will relieve the anemia when it is of the type mentioned above, but therapy must be directed also toward replacing the deficient enzyme of the pancreas, for the anemia is only a side-issue in the general pathologic process.

Megaloblastic anemia of infancy is probably caused by a deficiency of ascorbic acid and folic acid in unfortified processed milk diets.[27] An analogous situation has been induced in monkeys by this type of diet. Fortifying milk powder with ascorbic acid has almost eliminated infantile megaloblastic anemia. Ascorbic acid facilitates the conversion of folic acid to folinic acid and probably plays a role at other stages in the reaction which converts food folic acid to the active coenzyme form of this vitamin. This type of chemical interrelationship could not be established as an etiologic factor in the monkey anemia, but, rather, it appeared that the ascorbic acid deficiency, resulting in scurvy, acted as a stress factor increasing the need for folic acid. Nonetheless, the therapy of choice for this rare anemia of infancy is a combination of ascorbic and folic acids and a diet of broader nutritional value than milk alone. Usually vitamin B_{12} is ineffectual or induces only minimal response, even when given in high dosage.

Very occasionally, adult persons with severe scurvy will have megaloblastic anemia.[28] More frequently the anemia is normoblastic and unrelated to deficiency of one of the erythrocyte maturation factors. However, when it is megaloblastic, it probably has the same etiology as the megaloblastic anemia of infancy, a combined dietary insufficiency of ascorbic and folic acids. Limited experience with this type of anemia indicates that an adequate hematologic and antiscorbutic response will be obtained with ascorbic acid alone, though it would seem wise to give folic acid as well. Of course, dietary readjustment should be made to prevent recurrence of scurvy.

MEGALOBLASTIC ANEMIAS DUE TO METABOLIC ABNORMALITIES IN THE FOLIC ACID-ASCORBIC ACID SYSTEM

Occasionally megaloblastic anemia occurs in adults for reasons that are still obscure. The clinical features that differentiate these types from pernicious anemia are as follows: (1) the presence of free hydrochloric acid in the gastric secretions, (2) the absence of hemolytic jaundice, (3) the absence of spinal cord degenerative changes, and (4) the lack of response to vitamin B_{12} given either orally or parenterally. Diarrhea is usually not a prominent clinical feature, and steatorrhea does not occur. The diets consumed by these patients seldom have been deficient enough to explain the hematological picture.

One of these types is pernicious anemia of pregnancy,[29] which appears in the third trimester or may be found only after delivery. It is true that some women who develop this type of anemia have had episodes of severe vomiting during pregnancy and have eaten poorly because of this. It is plausible also that the requirements of the infant for erythrocyte maturation factors put a severe strain on the mother's supply. However, women develop this condition who have not vomited and who have eaten adequately. After pregnancy is over the anemia does not recur until a succeeding pregnancy. The response to folic acid is excellent, and Holly[30] has reported that vitamin B_{12} and ascorbic acid in combination also will induce a hematologic response, though neither alone is effective therapy. These considerations have led to the hypothesis that pregnancy in some way causes an abnormality in the chemical reaction which converts food folic acid to the folinic acid coenzyme. Oral folic acid is the therapy of choice.

Another type is achrestic (vitamin-B_{12}-refractory) anemia which occurs in men and in nonpregnant women[31] but is otherwise similar to pernicious anemia of pregnancy. The therapeutic response to folic or folinic acids is excellent, but, characteristically, treatment with vitamin B_{12} is ineffectual. In our clinic one patient with this condition did not respond to vitamin B_{12} and ascorbic acid, combined, though this combination has been said to be effective in pernicious anemia of pregnancy. Perhaps the defect in folic acid metabolism in achrestic anemia differs from that which is thought to be responsible for pernicious anemia of pregnancy. The therapy of choice is either folic or folinic acids.

Very occasionally megaloblastic anemia occurs which does not respond to folic acid, vitamin B_{12}, or ascorbic acid in any form or by any route of administration. As yet, there have been too few cases of this type to allow for any reasonable deductions regarding etiology. However, the fact that such types of megaloblastic anemia occur supports the contention that there are other factors beside folic acid and vitamin B_{12} necessary for the maturation of the erythrocyte. Occasional responses have been reported when crude liver extracts for oral use, autolyzed liver, and yeast preparations have been given to such patients. Two such patients who have been studied in our clinic failed to respond to all therapeutic measures except transfusions.¶

VARIATIONS IN BLOOD AND BONE MARROW PICTURE

As in all fields of medicine, no one hematologic feature always occurs in the anemias which have just been discussed. For instance, patients with sprue may occasionally have a normocytic normochromic anemia and yet may respond well to folic acid. This is true also of infants with megaloblastic anemia. Occasionally also, in any of these anemias, the bone marrow may not be frankly megaloblastic. The maturation defect may be evident primarily in the myeloid cells, as exemplified by the bizarre metamyelocyte, and yet the deficient erythrocyte maturation factor will induce a good hematologic response. These variations and vagaries must be kept in mind if errors in diagnosis and therapy are to be avoided.

¶ Mueller, J. F., and Vilter, R. W.: Unpublished data.

SPECIFIC THERAPEUTIC RECOMMENDATIONS

Patients with moderately severe uncomplicated pernicious anemia require only vitamin B_{12} or refined liver extract administered parenterally. Fifteen micrograms of the former or 15 U. S. P. units of the latter given daily for 10 days will induce a maximum hematological response, with at least a 15-fold safety factor. Vitamin B_{12} is cheaper and causes so few reactions that it is the preferred form of therapy. There is no evidence that liver extract will induce any better response than vitamin B_{12}; nor is there any evidence that folic acid, ascorbic acid, or iron is needed in the average case. Vitamin B_{12} by mouth in doses of 1000 to 5000γ daily or in much smaller doses, usually 15 to 25γ, combined with intrinsic factor will induce hematologic responses of varying degrees of adequacy in most patients with pernicious anemia, but these methods of therapy are uncertain and costly and are not recommended for practice. One oral U. S. P. unit of vitamin B_{12}-intrinsic factor combination determined by adequate therapeutic response in one patient with pernicious anemia in relapse may have a much lower potency in another patient with the same disease, because of absorptive difficulties.

When given by the parenteral route, as recommended above, vitamin B_{12} will induce a dramatic improvement in appetite and sense of well-being of the patient within 24 to 48 hours after administration has been started. Within three or four days, jaundice has disappeared, glossitis has improved, and reticulocytosis has begun and reaches a maximum level by the seventh or ninth day, falling off rapidly thereafter. Erythrocytes and hemoglobin begin to increase rapidly by the time the maximum reticulocyte response has been attained, and within three or four weeks the patient is normal hematologically. After the first 10 days of therapy, injections of vitamin B_{12} are usually given two or three times a week until the erythrocytes and hemoglobin are normal. Thereafter, the patient can be maintained by the injection of 20 to 30γ every three or four weeks.

Patients who have severe neurological degenerative disease or local or systemic infection require much more vitamin B_{12} or refined liver extract than has been recommended for the uncomplicated case. Under these circumstances, 50 or 100γ of vitamin B_{12} or U. S. P. units of refined liver extract should be given daily and the infection treated with an appropriate antibiotic. Under these circumstances or in a patient with extremely severe anemia, a transfusion may be needed to tide the patient over the critical period until specific therapy has begun to have its beneficial effect. The total volume of fluid administered should be kept as small as possible. Too much blood may be quite harmful, precipitating shock or pulmonary edema.

As soon as the infection is controlled, the vitamin B_{12} requirements fall into the range appropriate for the average case. Not so in the patient with severe neurologic disease. Under these circumstances, large doses should be continued three times a week for at least six months. Only thereafter can one be assured that maximum recovery has been attained. Once this maximum degree of recovery has been reached, it can be maintained on 20 to 30γ every three to four weeks, as in the average case, though most physicians prefer to use a larger dose in these patients. Actually, there is no good experimental evidence that such large doses are really necessary. In patients who developed neurologic relapse while being treated with folic acid, remissions have been induced rapidly with doses of vitamin B_{12} as low as 1γ daily.

If the patient has lost sufficient blood in the past to deplete his iron stores, he may develop hypochromia as his blood regenerates. This is the only indication for iron in pernicious anemia. Occasionally a patient with pernicious anemia, on maintenance therapy with vitamin B_{12}, may develop folic acid deficiency because of severe dietary inadequacy. This happens most frequently in chronic alcohol addicts. Under these circumstances macrocytic anemia recurs in spite of vitamin B_{12} therapy, or, if vitamin

B_{12} therapy has been discontinued by the patient, reinstitution of it may fail to have the desired effect. Such circumstances are the only real indication for folic acid in the treatment of pernicious anemia. Folic acid should never be used as the sole therapy, because of the danger of allowing rapid progression of severe neurologic degenerative disease.

A pernicious anemia patient's diet should have an adequate vitamin C content, as well as an adequate supply of protein and other essential nutrients. Supplementation with an excess of any of these substances is not necessary unless a severe deficiency of any one of them occurred during the development of pernicious anemia.

Raw or cooked liver or dilute hydrochloric acid is usually not necessary. Very occasionally, a patient with pernicious anemia continues to have diarrhea even after adequate treatment. Under these conditions, a large dose of dilute hydrochloric acid (4 to 8 cc.) in water sipped through a straw with meals may be helpful.

Dependent edema occurs frequently during the recovery phase of pernicious anemia, especially when the patient gets up to sit in a chair or walk. This edema is of no importance and will disappear spontaneously, since it is due to rapid increase in blood volume and other physiologic readjustments.

Patients with nutritional macrocytic anemia may be treated in the same way as those with pernicious anemia or may be given folic acid, 5 mg. three times daily by mouth. Of paramount importance is dietary improvement so that the patient eats an abundance of animal protein, green and yellow vegetables, and citrus fruits. In general, the hematologic response will be the same as described for pernicious anemia. If the patient continues to follow the improved diet, specific hemopoietic therapy may be discontinued as soon as the peripheral blood values have reached normal levels.

True sprue responds to folic acid, 5 mg. three times daily. Reticulocytosis occurs more slowly and the curve is flatter than that which one sees in patients with pernicious anemia treated with vitamin B_{12}. Normal hematologic values are attained in three to four weeks. Diarrhea subsides, steatorrhea is reduced, and absorption of all nutrients is improved, so that the oral glucose-tolerance test and vitamin A and E tolerance tests approach normal.[32] Patients with clinical symptoms of brief duration recover completely and usually require no further therapy than low-fat high-protein diet rich in B-complex vitamins and ascorbic acid. Patients with symptoms of longer duration than six months recover more slowly, may have recurring episodes of diarrhea and steatorrhea, and usually require maintenance therapy with folic acid, 5 mg. daily usually sufficing.

Vitamin B_{12}, given parenterally in doses larger than required in pernicious anemia, will usually induce a good response. Thirty micrograms daily are sufficient. However, it is uncertain whether vitamin B_{12} is sufficient to maintain all patients with longstanding sprue in good health for many years. Ultimately, supplementation with folic acid may be required.

Patients with idiopathic steatorrhea respond to 5 or 10 mg. of folic acid three times a day in an unpredictable fashion. Some are relieved of all their symptoms, including fatty diarrhea. Others, at the opposite end of the spectrum, show little or no improvement except for the relief of megaloblastosis and macrocytosis. The normocytic anemia may continue. These patients require severe restriction of dietary fat, high protein intake to relieve hypoproteinemic edema, calcium phosphate and viosterol to relieve tetany and osteomalacia, nicotinic acid, thiamine, and riboflavin to overcome deficiencies of these B-complex vitamins, and vitamin A as well. Even then, improvement may be quite unsatisfactory. Such cases of "refractory sprue" may be given a trial of cortisone,[33] 50 mg. every six hours for four or five days, then 25 mg. every six hours for three or four weeks. Unfortunately, even though striking improvement may have occurred at the onset of steroid therapy, as the dose is gradually reduced symptoms recur, sometimes in a severe form.

Patients with other diseases which interfere with absorption of nutrients from the gastrointestinal tract or who have steatorrhea on the basis of pancreatic insufficiency will be relieved of macrocytosis and megaloblastic maturation arrest in the bone marrow by folic acid, 5 to 10 mg. three times daily, but the other symptoms will be unchanged. Occasionally, however, the primary defect in absorption of foodstuffs may have induced such a severe deficiency of folic acid that diarrhea and steatorrhea have been accentuated. In such persons, there may be improvement in diarrhea and steatorrhea when folic acid is given.

Folic acid, 5 mg. three times daily, or folinic acid in twice this dose are the drugs to be used in achrestic anemia, pernicious anemia of pregnancy, or anemia associated with fistulous bowel communications, blind pouches, or gastrocolic fistulae. In the latter category vitamin B_{12} absorption may be so badly impaired that spinal cord damage may have occurred. Under these circumstances vitamin B_{12} must be given parenterally in doses of at least 15 to 30γ daily, and, after anemia and malnutrition have been controlled, corrective surgery must be carried out whenever possible. In the former categories folic acid must be continued until pregnancy terminates, or, in achrestic anemia, for the rest of the patient's life.

Infants with megaloblastic anemia should receive folic or folinic acids, 1 or 2 mg. three times daily, and ascorbic acid, 50 mg. three times daily. Broadening of their basic diet to include orange juice, cereals, dairy products, and meat products is equally essential. When this is accomplished and blood studies are normal, the folic acid can be discontinued.

Little can be added to what has already been said about specific treatment of refractory megaloblastic anemia. Transfusions of resuspended erythrocytes will be necessary to maintain the patient's erythrocytes and hemoglobin within safe limits. Among things that may be tried in addition to folic and folinic acids or vitamin B_{12}, which have failed, are chlortetracycline (Aureomycin), 250 mg. four times daily; crude liver extract, intramuscularly 3 to 5 cc. daily; Valentine's liver extract, 30 cc. three times daily by mouth; autolyzed liver in similar amounts. Administration of 100γ of vitamin B_{12} together with plasma or whole blood transfusions should be tried, to uncover the extremely rare patient lacking the vitamin-B_{12}-binding globulin in the serum. Clear-cut reticulocytosis and red blood cell increase following such a therapeutic combination will strongly suggest that one is dealing with this defect, if no such response was obtained previously when a similar dose of vitamin B_{12} was given alone.

MACROCYTIC NONMEGALOBLASTIC ANEMIAS

Macrocytosis of moderate degree may be found in some chronic anemias that are unrelated to the erythrocyte maturation factor deficiencies. This is the commonest type of anemia in patients with chronic liver disease who have not bled from hemorrhoids or esophageal varices.[34] The cause of the macrocytoses is obscure. The bone marrow is usually normoblastic, except in the occasional patient with dietary inadequacy in one of the erythrocyte maturation factors. Only under these circumstances, or when pernicious anemia or achrestic anemia are superimposed, will it be megaloblastic. The life span of the erythrocyte is shortened, as can be shown by Ashby or Cr^{51} technique,[35] and the erythrocytes contain more than a normal amount of water, but the way in which liver disease adversely affects bone marrow function or produces uniformly large erythrocytes has not been established. Only by improvement of liver function or by transfusions can the anemia be controlled. Liver extract, folic acid, vitamin B_{12}, or ascorbic acid have no specific beneficial effect, and iron is indicated only if there has been loss of blood. As liver function improves, remission gradually occurs in the anemia.

Patients with myxedema tend to have macrocytic erythrocytes, unless the blood loss of menorrhagia and metorrhagia induce a microcytic hypochromic picture. The bone marrow is usually inactive and at the normoblastic level of erythrocyte maturation. Only

when pernicious anemia or one of its relatives complicate the picture is it megaloblastic. The cause of the macrocytosis has not been explained. Treatment of the hypothyroid state results in remission of the anemia.

Acute and chronic hemolytic anemias tend to be macrocytic, because the numerous reticulocytes characteristic of the hemolytic state are very large cells. Control of the hemolytic process with corticotropin (ACTH), cortisone, or splenectomy controls the anemia, and macrocytosis disappears as reticulocytosis subsides.

Other chronic anemias, usually of the normocytic normochronic variety, tend to become slightly macrocytic the longer they last. Examples are the chronic hypoplastic anemia of severe long-standing malnutrition, the anemia of chronic renal disease and azotemia, and chronic aregenerative (refractory) anemia. None of these are caused by deficiencies of erythrocyte maturation factors; in none is the bone marrow megaloblastic, and treatment with these factors is of no avail. Only improvement in the primary disease or transfusions are of benefit.

Adult persons with scurvy, diagnostic rarities nowadays, usually are anemic. This anemia is usually slightly macrocytic unless complicated by external blood loss. The bone marrow usually is normoblastic, though, occasionally, as has already been noted, it may be megaloblastic. Infants with scurvy more commonly have the megaloblastic picture. When the marrow is normoblastic, the anemia is the result of vitamin C deficiency per se and is not caused by the indirect effect of vitamin C lack on the availability of the erythrocyte maturation factors. When the marrow is normoblastic, the cause of the anemia is either blood loss into the tissues, or an inhibition of bone marrow activity due to vitamin C lack, or both. Under either circumstance, ascorbic acid will relieve the scurvy and the anemia. Folic acid or vitamin B_{12} have no effect.

SUMMARY

Macrocytic megaloblastic anemia may be caused by conditioned deficiencies of vitamin B_{12}, dietary insufficiency of vitamin B_{12} or the folic acid-ascorbic acid system, metabolic abnormalities in the folic acid-ascorbic acid system, and unknown factors.

It is probable that each of these conditions is due to an abnormality in the chemical chain reaction which is necessary for the formation of the nucleic acids, particularly the deoxyribose-containing type.

Vitamin B_{12} and folinic acid are catalysts in the reaction and when deficient are responsible for the occurrence of these anemias.

Accurate diagnosis is essential in order that the correct therapeutic tool may be selected and supportive therapy of the correct type administered.

Macrocytosis may also occur during the course of chronic liver disease, hypothyroidism, refractory or aregenerative anemia, hypoplastic anemia, or chronic hemolytic anemia. The bone marrow is not megaloblastic, and the hemopoietic vitamins are valueless unless a secondary deficiency of one of them has occurred. Here, too, therapeutic trials with various vitamin mixtures can never take the place of accurate diagnosis.

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News and Comment

ANNOUNCEMENTS

Residencies in Psychiatry.—The Veterans Administration Hospital, Lyons, N. J., has available residencies in Psychiatry for a one- to three-year period, which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences, and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals and clinics in the adjacent area. There is, in addition, a series of extensive guest lecturers as well as an Annual Institute at the hospital. Training may commence at any time.

American Institute of Dental Medicine Meeting.—The next Annual Meeting of the Institute will take place at the Desert Inn, Palm Springs, Calif., Oct. 23-27, 1955. The faculty will consist of the following:

Maury Massler, D.D.S., M.S., University of Illinois, Chicago: Effects of filling materials on the pulp; sterilization of dentin; tissue changes during ageing.

Valy Menkin, M.D., Temple University Medical School, Philadelphia: Inflammation, bacterial invasiveness, and immunity; chemical factors liberated by injured cells in inflammatory exudates; the anti-inflammatory problem with particular emphasis on the mechanism concerned, as induced by corticosteroids.

Hans Selye, M.D., University of Montreal, Montreal, Canada: Recent progress in the study of stress as applied to dental medicine.

Reidar F. Sognnaes, D.M.D., Ph.D., Harvard School of Dental Medicine, Boston: Relative significance of cellular and chemical remodeling of bones and teeth as revealed by radioactive isotopes; the complexity of the caries problem suggested by recent observations in experimental animals; the clinical implications of experimental caries research.

Wendell L. Wylie, D.D.S., University of California, San Francisco: Tooth guidance and factors influencing the rate of eruption.

All Seminar lecturers will participate in a round table forum discussing the application of their subject to the practice of dental medicine. Applications and full information may be secured from the Executive Secretary, Miss Marion G. Lewis, 2240 Channing Way, Berkeley 4, Calif.

International Academy of Proctology Meeting.—The 7th annual meeting of the International Academy of Proctology will be held March 23 through 26, in New York City.

Panel discussions on cancer of the lower intestine and on ulcerative colitis will highlight the Academy's scientific sessions, at the Hotel Plaza, in New York City, on March 23, 25, and 26, and at the Jersey City Medical Center, on March 24.

Operating clinics and a symposium on intestinal surgery and related conditions will be given by members of the Jersey City Medical Center. A special group of film demonstrations will be presented in a visual education session.

In accordance with its established practice, the Academy extends an invitation to all physicians to attend its sessions, and the American Academy of General Practice will grant credits to its members attending the meeting.

American Goiter Association Meeting.—The 1955 meeting of the American Goiter Association will be held in the Skirvin Hotel, Oklahoma City, Okla., April 28, 29, and 30, 1955.

The program for the three-day meeting will consist of papers and discussions dealing with the physiology and diseases of the thyroid gland. Inquiries may be sent to John C. McClintock, M.D., Secretary, 149½ Washington Ave., Albany, N. Y.

PERSONAL

Madison, Wis.—The University of Wisconsin regents Saturday approved an interim appointment of Dr. Otto A. Mortensen to the post of acting dean of the University of Wisconsin Medical School from March 1 to June 30. He is now associate dean of the school.

In a parallel action, the regents granted Dean William S. Middleton a one-year leave of absence, effective March 1, to permit him to become chief medical director of the U. S. Veterans Administration at that time.

Before his call to the federal agency, Dean Middleton had resigned his Medical School deanship, effective July 1, to devote his energies to research and teaching. Dr. John Z. Bowers, now dean of the University of Utah College of Medicine, is scheduled to take over the Wisconsin Medical School deanship July 1.

Dr. Hobart A. Reimann.—Dr. Hobart A. Reimann has been appointed Visiting Professor of Medicine at the University of Indonesia Faculty of Medicine in Djakarta, Java. Dr. Reimann's appointment is in connection with an affiliation between the University of California School of Medicine, San Francisco, and the Faculty of Medicine at Djakarta and is underwritten by the Foreign Operations Administration. He will act in a consultant, teaching, and advisory capacity. The medical school in Djakarta was built by the Dutch and is equipped as a modern institution staffed by Indonesians and visiting American faculty members. En route to Java, Dr. Reimann will address the Medical Society of Honolulu and will visit the medical schools in Tainan, Formosa, and in Manila. Dr. Reimann recently returned from Lebanon after a two-year tenure as Professor of Medicine at the American University at Beirut.

Books

Physiology and Biochemistry of the Skin. By Stephen Rothman, M.D. Price, $19.50. Pp. 741. University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1954.

This book, with 741 pages, is the first comprehensive and thorough presentation of physiology and biochemistry of the skin in the English language and should be on the desk or available for reference to any internist as well as to dermatologists and other physicians or research workers interested in the subject or in the close relationship that physicochemical changes in the skin bear to internal or systemic disease. Whereas Dr. Rothman in the foreword stated, "The main purpose of this book is to serve dermatological research," there is a great deal in the book that is of fundamental basic character, which the clinician should be familiar with, let alone a scientist working on some problem in medicine as a whole. There are numerous references to the physicochemical aspects of various dermatoses often associated with systemic disease. The author has, however, purposely refrained from making the book a text on clinical dermatology. He also has avoided, with a few exceptions, recapitulation of facts that can be found in current texts on physiology and biochemistry, as for example the discussion of biochemistry of nucleoproteins, because the latter have not been shown to behave differently in the skin from the way they do in other organs.

The author presents both the old and the newer studies in the field of physiology and biochemistry of the skin, including extensive research of his own in this field over the past 25 years, for which he is internationally known. He fairly presents controversial points of view in concise statements. He also emphasizes that there are many problems that have only been touched on and that remain to be solved in this relatively young branch of the clinical sciences. Dr. Rothman is fortunate in having young contributors, who were trained by him and who were or still are members of his staff at the University of Chicago, namely, Drs. Z. Felsher, P. Plesch, G. C. Wells, and A. Lorincz. There also are chapters by Drs. A. B. Lerner and H. Pinkus. All of the contributors are well known for their research work on physiology and chemistry of the skin.

The author and publisher have done an outstanding job on the format of the book. The figures, charts, drawings, and photomicrographs are all of excellent quality. The table of contents at the beginning of each chapter is of value in orientation, as is the bibliography arranged alphabetically and also by numbers at the end of each chapter. The subject index, indicating where certain chemical substances or conditions are considered in the text, together with an author index, makes this book an excellent one for reference to any subject. The

author and his contributors give a great many references to articles in biomedical periodicals and various journals consisting purely of research, as well as to journals in dermatology and internal medicine.

Rothman's book is to be recommended unreservedly to all physicians and research workers interested in any phase of the physiology and biochemistry of the skin.

An Rh-Hr Syllabus: The Types and Their Applications. By Alexander S. Wiener, M.D. Price, $11.50. Pp. 763. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1954.

This book is, in the author's words, (a collection) "in one volume (of) the author's most representative and important contributions to this subject, thus giving an idea of how knowledge in this field developed." True to his purpose, the author has selected 72 of his and his associates' papers (of the 333 written at the time of the publication of this book) and has integrated them into a history of the development of knowledge of the Rh-Hr blood types. These articles are reproduced from the various journals in which they were published in their original form and type, with the addition of editorial notes to clarify changing nomenclature and concepts. One section of the book deals with techniques of tests employed in Rh-Hr blood typing work and has apparently not been published previously.

A compilation of one author's contributions to a field in investigation, however considerable such contributions may be, as in the case of Dr. Wiener, would seem to have most value only to those persons fully versed in the contributions of other authors in the field. The casual reader, unschooled in the works of Levine, Fisher, Race, Mourant, Sanger, and others and learning of their work only from the prolific pen of Dr. Wiener would hardly appreciate the broad view of the Rh "cold war."

Another possible benefit to those investigators working with Rh problems would be the presentation for the first time of some of the author's articles which have appeared in periodicals of limited circulation and so may have heretofore been unavailable. The inclusion of certain letters to the editor and correspondence without the original article under criticism or rebuttal statements (except in one instance) serves only as a limited source of historical enlightenment.

Therefore, this book can be recommended as a source of the best contributions of the author to the field of the Rh-Hr blood types only to those persons whose background in this subject will permit critical appraisal of its contents. It can not be recommended to the technician or casual reader except for its bibliography and for appreciation of the tremendous number of contributions the author has made to this field.

Cancer: Race and Geography. By Paul E. Steiner, Ph.D., M.D. Price, not given. Pp. 363, with 73 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1954.

The data for this study are based on a review of the 35,293 necropsies performed at the Los Angeles County Hospital over the 30-year period 1918 through 1947. In 6,072, or 17.2%, of these necropsies malignant tumors were found. Fifty-three types of cancer were listed, and to each of the 20 commonest varieties the author has devoted a chapter. Within each chapter one finds a statistical analysis of the racial differences, a discussion of the effect of environment and heredity, a demonstration of the tumors that exhibit biologic differences associated with race, and a discussion of the etiologic implications based on the observed statistical and biologic facts. Some 50 tables and 73 figures are assembled in the book to provide a basis for the summaries and conclusions reached by the author. As stated, "the detection of new etiological relationships and the stimulation of new ideas was the goal." He is aware of the shortcomings of the data but hopes that this work will provide an impetus for further investigations. The current great interest in the increase of reported death rates from cancer, in relation to smoking and other environmental factors, should make this account an important and timely contribution.

Principles of Internal Medicine. Edited by T. R. Harrison and others. Price, $16.00. Pp. 1,703, freely illustrated. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1954.

This is the second edition of an immensely popular and useful book which has become a necessity for all teachers of internal medicine and a constantly used reference for all internists who are making an honest attempt to keep up with advances in their specialty. Because of the nature of the material presented, it is not surprising that a new edition was required four years after the initial publication.

For those accustomed to traditional textbooks of medicine there will be some difficulty in gaining information on a given point or a given disease quickly. However, having gained familiarity with the emphases and arrangement of the material the reader will find his excursions into the subject matter very rewarding. In the preface the following statement appears: "Depending on the nature of the clinical problem, the most effective use of the book will naturally vary. In general, it is suggested that the reader first peruse the chapter or chapters which deal with the patient's major complaints. Having obtained from the discussions of differential diagnosis in these chapters on manifestations an idea as to the most likely two or three basic disorders which may be responsible for the patient's complaints, the reader may then turn to the back of the book and read the discussion of these several diseases. In many instances he will find that there will also be an advantage in going over certain chapters which are concerned with the mechanisms of these diseases."

Obviously this is no quick or superficial approach to medical knowledge. The first 497 pages are devoted to an exposition of the mechanisms underlying the cardinal manifestations of disease, such as pain, fever, shortness of breath, cough, indigestion, jaundice, edema, alterations in weight, anemia, etc. Then follows a section on the general principles of treatment, after which specific disorders of metabolism, diseases due to biologic agents, diseases associated with reactions to stress and antigenic agents, and specific derangements of different organ systems of the body are discussed.

There is a notable lack of the repetition one might expect in a book so arranged. Hence the reader who has not waded through the lengthy discussions of the first sections may find the information gleaned from accounts of specific diseases somewhat incomplete.

On the whole, however, the 87 contributors, whose communications have been ably edited by a good board, composed of Raymond D. Adams, Paul B. Beeson, William H. Resnik, George W. Thorn, and M. M. Wintrobe along with Tinsley Harrison, the chief editor, have produced a notable fund of medical information. The reader can hardly avoid being stimulated to think about his patient. This obviously is the goal of the editors.

Connective Tissue in Health and Disease. Edited by G. Asboe-Hansen, M.D. Price, $7.50. Pp. 321, with 83 illustrations. Ejnar Munksgaards Forlag, Nørregade 6, Copenhagen, K, 1954.

Connective tissue and ground substances are vexing in their complexity, and with the vast array of newer techniques this no longer neglected medical area is increasingly confusing. Asboe-Hansen's book, contributed to by 23 investigators from different parts of the world, is an attempt to bring the subject up to date. The advent of powerful steroid hormones; advances in morphology, chemistry, and physiology; the introduction of the electron microscope; the newer enzymatic approaches—all are displayed against the clinical confusion of the amorphous conglomerate of "collagen diseases" and the speculative system of Selye and the "alarm reaction." In fact, the subject covers every medical specialty, touches every clinical problem, and concerns all organs and systems of the body.

The book is excellently made. The individual sections are very well written, although with some unevenness. A good deal of overlapping is necessary, since each section is an independent unit. The grave fault which renders this book much less useful than it would otherwise be is the lack of an index. This is made up for only in small part by a table of contents. Very few except specialists working in the particular field will read the book straight through. Its main value is as a reference book, this value being largely diminished because it has no index. Furthermore, the value of the numerous references at the end of each chapter is seriously undermined by the failure to give the title of the articles. This is all very well when an author himself is quoted or when the reader is thoroughly conversant with the literature. However, this book's main appeal should be to those not too familiar with the field, and the value of a bibliography or a list of references without the title of the work is for the novice approximately as useful as browsing through the telephone directory of a distant city in a foreign language. Some day writers and publishers will recognize that the additional labor and cost of giving titles to references amply pay for themselves in the increased usefulness of the book. For those willing to read the book from cover to cover there is a great reward. Indeed anyone looking for a particular fact may have to do just that to find it.

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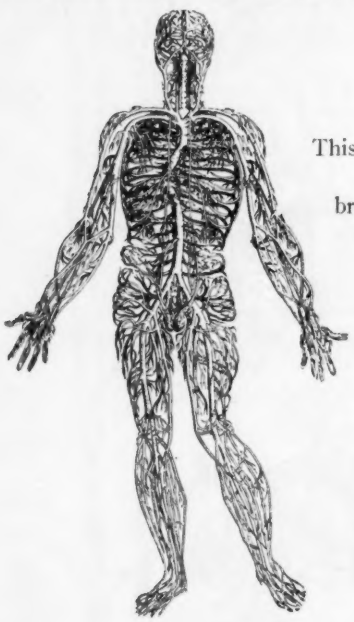

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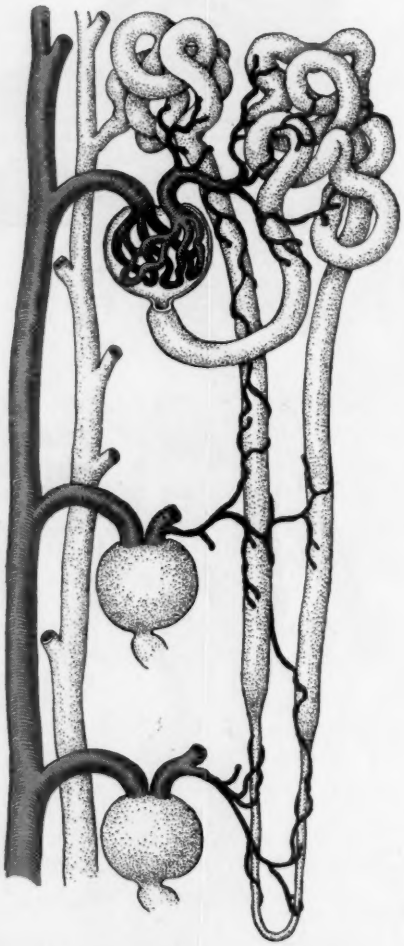

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1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

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Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

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Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.

Svartz, N.: Acta Med. Scandinav. 141:172, 1951.

1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.

Morrison, L. M.: Gastroenterology 21:133, 1952.

1953 Morrison publishes results from a series of 47 patients treated with Azulfidine compared to a control series of 60 patients receiving other current therapy: In the Azulfidine-series 18% are symptom-free and 52% improved, compared to 5% and 32% respectively, in the control series.

J. A. M. A.: 151:366 (Jan. 31) 1953.

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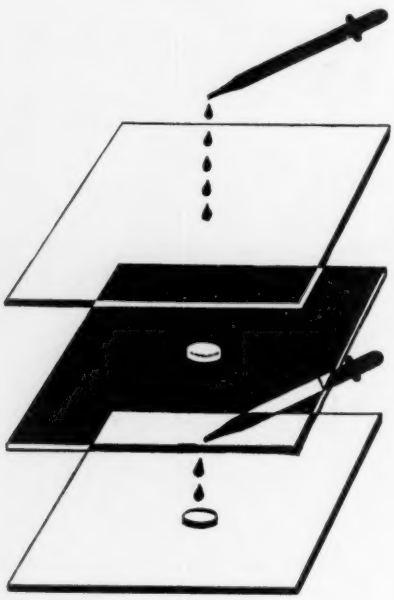

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Packaging: Bottle of 90 Reagent Tablets with Test Mats.

*Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, ed. 3, Philadelphia, Lea & Febiger, 1953, vol. 1, p. 485.

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